MEETING

OF

SCIENTIFIC WORKSHOP ON

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

Conducted by Sara Eggers, PhD,

Office of Strategic Programs (OSP), CDER, FDA

Monday, October 24, 2016

10:03 a.m.

Food and Drug Administration (FDA)

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Reported by: Erick McNair, RPR/CSR,

Capital Reporting Company

A P P E A R A N C E S

Sara Eggers, PhD
Office of Strategic Programs (OSP), CDER, FDA
Kendall Marcus, MD
Director, Division of Dermatology and Dental Products (DDDP), CDER, FDA
Henry Lim, MD
Chair, Department of Dermatology, Henry Ford Hospital
Joyce Teng, MD, PhD
J. Paul Phillips, MS
DDDP, CDER, FDA
Kathryn O'Connell, MD, PhD
Rare Diseases Program, CDER, FDA
Elisabeth Minder, MD
Julie Beitz, Director, Office of Drug Evaluation 3
Jill Lindstrom, Deputy Director
Division of Dermatology and Dental Products
Roselyn Epps, Medical Officer
Division of Dermatology and Dental Products
Snezana Trajkovic, Clinical Team Leader
Division of Dermatology and Dental Products

A P P E A R A N C E S (continued)

Jonathan Goldsmith, Associate Director,
Rare Diseases Program, CDER
Electra Papadopoulos, Acting Associate Director
Clinical Outcome Assessments Staff, CDER
Meghana Chalasani, Office of Strategic Programs
Pujita Vaidya, Office of Strategic Programs
Graham Thompson, Office of Strategic Programs
Laurie, Office of Strategic Programs
Richard, Office of Strategic Programs
Maureen Poh-Fitzpatrick, MD
Columbia University
Robert Desnick, MD
Mount Sinai School of Medicine
Manisha Balwani, Co-director
Porphyria Center, Mount Sinai School of Medicine
Madelyn Harvard
Andrew Turell
Jay Goddu
Hannah Watkoske
Brady Weeden
Leslie Silvey

A P P E A R A N C E S (continued)

Cortney Madden

Michael Ferry

Steve Ferry

Michael Olscher

Sue Ellen Phillips

Jasmin Barman-Aksoezen

Patricia Bestechen

Nanelle Taylor

Paul Hugo

Becky Griffiths

Ginger Honiker

Sue Gore

Kerry Wiles

Victor Mejias

Madeline Harvard

Meghan Rohn

Tim Sanders

Rocio Sanders

Tracy Leach

Jennifer Beck

Cheryl Crites

A P P E A R A N C E S (continued)

Denise Edwards

Candace Colbert

Kate Sheffield

Shellie Miller

Joe Lewis

Diana Ijames

Rocco Dambro

Olivia Donaghy

Julianna Amodei

Ashley Eskew

Nick Guanciale

Theresa Lester

Tom Foley

Monica Foley Fleegel

Shawn Willis

Alex Baria

Rachel Wise

Jere Wise

Rob Saupe

Pierre Mouledoux

Hannah Peterson

A P P E A R A N C E S (continued)

Martha Peterson

Lachlan

David Garrett

Michael Kinworthy

Betty Resich

Menno Peters

Darlene Burton

Gail Evans

Tim Hussey

Ben McKillop, Spokesperson, Morgan McKillop

Barbara Morris

Rebecca Bittner

John Crandall

Mitchell Felts

# C O N T E N T S

P R O C E E D I N G S

DR. EGGERS: All right. Even though we are not -- oh, we are not completely -- we still have people milling about, we are going to get started because we have a lot to cover today. This is an important meeting.

Good morning, everyone. I'm Sara Eggers. I'm from FDA, Office of Strategic Programs in the Center for Drugs. And I am amazed by this turnout. This is stellar. But this is an exciting day for us. We are grateful that you have traveled.

And I'm going to let Dr. Marcus give some proper welcoming remarks. But as the facilitator of today's meeting, please let us know if you need anything.

I'm going to go through a few housekeeping things in a little bit. But before I do that, let's turn to hear who's here from FDA. These are all of my FDA colleagues, and I'm going to ask you to go through and just state your name and your role here at FDA. We'll start with Julie.

DR. BEITZ: Hi. My name is Julie Beitz.

I'm the director of the Office of Drug Evaluation 3.

DR. MARCUS: Good morning. I'm Kendall Marcus, the director of the Division of Dermatology and Dental Products.

MS. LINDSTROM: Good morning. Jill Lindstrom, the deputy director of the Division of Dermatology and Dental Products.

MS. EPPS: Good morning. I'm Roselyn Epps. I'm a medical officer in the Division of Dermatology and Dental Products.

MS. TRAJKOVIC: Good morning. Snezana Trajkovic, Clinical Team Leader, Division of Dermatology and Dental Products.

MR. GOLDSMITH: Hi. Good morning. My name is Jonathan Goldsmith. I'm the associate director of the Rare Diseases Program in CDER.

DR. O'CONNELL: Good morning. My name is Kathryn O'Connell. I'm a medical officer in the program Rare Diseases Program with Jonathan.

DR. PAPADOPOULOS: Good morning. I'm Electra Papadopoulos, and I'm the acting associate director for Clinical Outcome Assessments staff in

CDER.

DR. EGGERS: Okay. And then over here we have my colleagues from the Office of Strategic Programs.

MS. CHALASANI: Meghana Chalasani.

MS. VAIDYA: Pujita Vaidya.

MR. THOMPSON: Graham Thompson.

DR. EGGERS: And someone else?

MS. VAIDYA: We have Laurie (ph) and …

DR. EGGERS: Oh, Laurie?

MS. VAIDYA: Yeah.

DR. EGGERS: Laurie, raise your hand.

And we have Richard (ph). Raise your hand, please.

If you've got any questions, we're the ones to come find.

And now let's go around and find out who is here with EPP. So we're just going to go through around the table, and if you can state your name and where you're from. I think, okay, we'll start.

MR. TURELL: Hello, everyone. My name's Andrew Turell. I'm from New York, really happy to be

here.

MR. GODDU: Hello, everybody. I'm Jay Goddu. I'm from Connecticut.

MS. WATKOSKE: Hi. I'm Hannah Watkoske. I'm from Atlanta, Georgia.

MR. WEEDEN: I'm Brady Weeden. I'm from here.

(Laughter.)

MS. SILVEY: I'm Leslie Silvey. I'm from Texas.

MS. MADDEN: I'm Cortney Madden. I'm from South Carolina.

MR. M. FERRY: Good morning. Michael Ferry from the State of Washington.

MR. S. FERRY: Steve Ferry, Virginia.

MR. OLSCHER: Michael Olscher, Warkworth, Ontario.

MS. PHILLIPS: Sue Ellen Phillips from Michigan.

MS. BARMAN-AKSOEZEN: Jasmin Barman-Aksoezen from Switzerland.

MS. BESTECHEN: Hi. My name is Patricia

Bestechen, and I'm from Dover, Delaware.

MS. TAYLOR: Hi. My name is Nanelle Taylor, and I'm from Chico, California.

MR. HUGO: Hi. My name's Paul Hugo. I'm from St. Paul, Minnesota.

MS. GRIFFITHS: Hello. My name is Becky Griffiths. I'm from Massachusetts.

MS. HONIKER: My name is Ginger Honiker, and I'm from Boston, Massachusetts.

MS. GORE: I'm Sue Gore. I'm from St. Paul, Minnesota.

MS. WILES: Kerry Wiles, Omaha, Nebraska.

MR. MEJIAS: Hello. Good morning. Victor Mejias from Chicago, Illinois. Go Cubs.

(Laughter.)

MS. HARVARD: Madelyn Harvard, Memphis, Tennessee.

MS. ROHN: My name is Meghan Rohn. I'm from Midland, Michigan.

MR. T. SANDERS: Tim Sanders. Satellite Beach, Florida.

MS. R. SANDERS: Rocio Sanders from

Satellite Beach, Florida.

MS. LEACH: Tracy Leach from Pennsylvania.

MS. BECK: Jennifer Beck from Connecticut.

MS. CRITES: Cheryl Crites from Michigan.

MS. EDWARDS: Denise Edwards from Michigan.

MS. COLBERT: Candace Colbert, Boston, Massachusetts.

MS. SHEFFIELD: Kate Sheffield. I'm from Georgia.

MS. MILLER: Shellie Miller, Denver, Colorado.

MR. LEWIS: Joe Lewis, Lideman (ph), Virginia.

MS. IJAMES: Diana Ijames, Missouri.

MR. DAMBRO: Rocco Dambro, Westchester, Pennsylvania.

MS. DONAGHY: Olivia Donaghy, Orlando, Florida.

MS. AMODEI: Julianna Amodei, and I'm from Syracuse, New York.

MS. ESKEW: Ashley Eskew, South Carolina.

MR. GUANCIALE: Nick Guanciale from

Syracuse, New York.

MS. LESTER: Theresa Lester from Southern Minnesota.

MR. FOLEY: I'm Tom Foley from Courtland, Minnesota.

MS. FOLEY FLEEGEL: Monica Foley Fleegel from Loveland, Colorado.

MR. WILLIS: Good morning. Shawn Willis from Burlington, North Carolina.

MR. BARIA: Alexia Baria, Chicago, Illinois.

MS. WISE: Rachel Wise, Philadelphia, Pennsylvania.

MR. WISE: Jere Wise from Bethany Beach, Delaware.

MR. SAUPE: Rob Saupe, Coeur d'Alene, Idaho.

MR. MOULDEDOUX: Pierre Mouledoux from New Orleans.

MS. H. PETERSON: Hannah Peterson from Washington, D.C.

MS. M. PETERSON: Martha Peterson, Chatham, New Jersey.

MS. LACHLAN: Lachlan (ph) from Boston,

Massachusetts.

MR. GARRETT: David Garrett from Fort Worth, Texas, where the West begins. And I'll speak. Michael Kinworthy (ph) will be here later from Reston, Virginia. He had to work this morning.

MS. RESICH: Betty Resich from Fort Worth, Texas.

MR. PETERS: Menno Peters, Stratford, Ontario, Canada.

MS. BURTON: Darlene Burton, Corpus Christi, Texas.

MS. EVANS: Gail Evans, Bowie, Texas.

MR. HUSSEY: Tim Hussey, Atlanta, Georgia.

MR. MCKILLOP: I'm Ben McKillop, spokesperson from Morgan McKillop, Long Island, New York.

MS. MORRIS: Barbara Morris from Berlin, Maryland.

MS. BITTNER: Rebecca Bittner from Philadelphia, Pennsylvania.

MR. CRANDALL: John Crandall from Cincinnati, Ohio.

MR. FELTS: Mitchell Felts from Cincinnati, Ohio.

DR. EGGERS: We miss anyone? Wow.

Let's give a round of applause for you to come here, for your dedication.

(Applause.)

DR. EGGERS: And we thank you.

I didn't hear anyone from Iowa, but there are -- that's where I'm from. But I did hear a lot from Minnesota and Illinois.

So let's go through what the agenda is. This is a very full day. This is a novel approach that we are taking to a type of scientific workshop, bringing together the patients to provide their perspectives with experts to provide more of the scientific perspective on things.

The morning before lunch, we'll focus on hearing from you, people living with EPP. We're going to start with a brief overview of EPP and current treatment approaches to make sure we're all on the same page with the background.

And then we're going to move into, first, a

set of panel comments to kick off a facilitated dialogue. But we're going to come and do really town hall-style discussion today. I'll give a little bit more detail about that in a few minutes.

There is a chance for open public comment. And open public comment is a chance to talk to -- if there are things that you want to share that are outside the scope of our discussion this morning. Our discussion is really focused on the health effects of EPP and your experiences and general perspectives on treatment approaches generally.

So if you have a specific comment -- and it can be not just the patients or patient representatives, caregivers and others, parents, it can also be others in the audience here today. So we have one open public comment in the morning time and one in the afternoon.

If we do not have -- if you feel that you don't need to give open public comment, we will fill that time with the facilitated dialogue. I think the signup for that was in the registration. If we don't get to you in the morning, we'll get to you in the

afternoon.

After lunch -- let me tell you a little bit about lunch. Most of you preordered your lunch. I believe they're going to then be set in the -- on those back tables there, and you can grab your lunch, each at your table, the round table, or the back table, whatever makes you -- wherever you would like.

After lunch, we will have a presentation giving the overview of FDA's role, our regulatory process, followed by a panel discussion with experts on scientific aspects of clinical trial design for EPP.

But we are going to try our best to get as much patient perspective through some polling questions and other things into that discussion this afternoon. Again, there's another time for open public comment, and then we will end the day.

A few housekeeping remarks. The restrooms are outside. If you go at the foyer -- that's the other side of this meeting room -- and you find that hallway, that's the end. Take the hallway all the way down. The restrooms are on your left.

Please feel free to get up at any time. We don't have any scheduled breaks before our lunch at 12:30, but we encourage you to get up as you need. If you need to walk around, whatever you need to do, please feel comfortable. This is an informal meeting setup.

This meeting is being webcast, and we thank -- we have robust participation on the web as well. The meeting is going to be transcribed, recorded, and put up on our website in a few days after the meeting. There will also be a transcript of the meeting.

With that, I think I've given all the housekeeping remarks that I should, and I'm going to turn it over to Kendall to give some welcoming remarks.

Oops.

DR. MARCUS: Good morning. As I've already introduced myself, I'll just repeat in case you didn't catch my name. I'm Kendall Marcus. I'm the director of the Division of Dermatology and Dental Products. We regulate products that are developed for the treatment of EPP.

I want to welcome all of you in the audience as well as our participants who are participating remotely. I have to say it's really awe inspiring for me to see so many of you in the room today, particularly having read as many of the letters that I've received as I have been able to.

And to understand the difficulties that you encounter even navigating your own homes, I have to say it is just remarkable to me the efforts that I am sure all of you went through in order to be able to participate today.

I really see this as an exciting opportunity for us to engage with you in both patient-focused and scientific discussions. As Sara already mentioned, this represents a novel approach for us to engage in both conversations with you.

I'm just going to briefly touch on my own background. I am trained in infectious diseases, and I spent many years in the Division of Antiviral Products here at FDA. And I've really seen how engagement of patients, care providers, drug companies, and the FDA collaboratively can result in

innovation and transform medical care for patients who are in great need of products to help manage their disease.

I understand very clearly, again from your letters, the tremendous impacts that your disease can have on your physical health as well as your mental health and the tremendous social impact that it has on you in just day-to-day functioning and choice of careers and ability to engage in activities with friends and family.

Our discussions today are intended to focus on the broader issues that are related to drug development for EPP, and I just would like to mention that we won't be discussing any specific technical regulatory or development aspects of any single product today.

We don't expect to come out of the workshop having identified particular drugs for study, nor to map out specific development programs for any particular drug product. It is our responsibility to ensure that the benefit of a drug outweighs its risk.

So having this kind of dialogue with you is

extremely invaluable for us to hear about what you care about most and what can help you out and what can help us lead the way in figuring out how to best facilitate drug development for EPP and understand how patients view the benefits and the risks of treatment for EPP.

I just would also like to point out that we have a number of drug developers as well as researchers and healthcare providers participating -- excuse me -- as well as patients and care providers.

As I've touched on already, FDA plays a critical role in development, but we are just one part of the process. I really believe it's when all stakeholders are actively engaged that true innovations and real breakthroughs can be achieved.

I just want to reiterate again that we protect and promote public health by evaluating the safety and effectiveness and the quality of new drugs, but we don't develop drugs and we don't conduct the clinical trials. Drug companies, sometimes working with researchers and patient communities, are the ones who conduct trials and submit applications for new

drugs to the FDA. It is then our responsibility to ensure that the benefits outweigh the risks.

We'll be having some presentations in the afternoon in order that -- in order to help you all better understand our process. As I just mentioned, we don't direct drug development, and I think that that's one of the common misconceptions people have about FDA.

We don't tell researchers what to work on. We only regulate the development process. The benefit-risk decision-making process is an integral part of our review process, and we really look forward to incorporating what we learn today from you into our thinking and our understanding of how you all view the benefits and the risks of EPP treatments.

Just once again, I'd like to say we're all here today to hear your voices, the voice of the patients. And we thank you tremendously for your participation. We're grateful to each and every one of you for being here and for your willingness to share your personal stories with us, your experiences, and your perspectives.

I will now turn the podium over to Dr. Henry Lim, and he will provide us with a background on the epidemiology and the natural history of EPP.

I would just like to point out that we are doing these introductory talks in order that everybody in the audience can be on the same page going into these discussions as best as possible.

I have many members of my division here who may know more or less about EPP, and I would really like us all to get onto the same page as we move into discussion of patient perspectives and impacts.

Thank you.

DR. LIM: Thank you, Kendall. Thank you very much for inviting me to participate in the session today.

I'm Henry Lim. I'm at the Henry Ford Hospital in Detroit, Michigan. My connection to EPP started when I was a resident in training at NYU many, many years ago. I did some laboratory work on the activation and the complement system by protoporphyrin, work some with Maureen Poh, who is in the room right now, and I continued on my interest

since then to cover photo-dermatology, in general, including the porphyrias, of course.

So the task today is, for me at least, to cover the epidemiology and natural history of EPP. This is my disclosure slide. The part that I want to highlight is that I am -- or I was one of the investigators when we -- with Clemovel (ph) in looking at alfamelanotide for EPP. That paper, as you all know, has been published in New England Journal of Medicine.

So I want to cover, essentially, EPP in general in terms of natural history, speaking to this very sophisticated and directly involved and engaged audience.

We know -- we all know that EPP starts in childhood. Most patients would complain about burning and stinging sensation without any cutaneous changes, but a few hours later there would be redness as well as swelling as well as a development of hive-like spots on the sun-exposed area.

The last bullet there is quite rare. The late onset of EPP has been reported. I have seen one

or two patients with that, usually associated with myelodysplasia. So probably for this -- for the purposes of today's talk, we will focus on the EPP itself.

Just to make sure that we're all on the same page, you know, when we talk about EPP, the thing we need to understand, a little bit about the biosynthetic pathway of hemoglobin, which is the bottom line.

Do I have a pointer here? Let's see. Okay.

It is the biosynthesis of hemoglobin, which is -- the last one is Hem (ph). It starts with this chemical called aminolaevulinic acid through various successive enzymatic step. Eventually Hem is formed.

The problem with EPP -- again, many of you -- I'm sure all of you, actually, know about this -- is that there is a decrease in the enzyme called ferrochelatase. Because of decrease in the enzyme, there is an elevation of the protoporphyrin. And this would result in the development of erythropoietic protoporphyria.

The main reason is a protoporphyrin ESA,

photosensitized, meaning if you expose anybody to protoporphyrin and give them enough protoporphyrin, expose them to light, they would develop essentially skin reaction, what we call phototoxic reaction.

So in terms of prevalence of EPP, you could see that -- this is from the literature -- Japan has very high prevalence. In the European countries, usually it's about 1 per 100,000.

The interesting part is that looking at the data from South Africa, the general populations, the prevalence is quite low while the European immigrant population in South Africa, it is closer to the European prevalence, indicating that in African -- individuals of African descent, the prevalence of EPP is very, very low. I think that is true throughout the world. In the U.S., we'd rarely see anybody with African descent with EPP.

So the best paper on the natural history on EPP in terms of the largest number of patients is the one that I'm going to cite here, which is the study from Alex Samsi (ph) and Badminton Group from Cardiff in Wales. They looked at almost 400 living EPP

subjects in their patient population.

In their cohort, you could see that 223 of them were investigated, consisting of about the same ratio of male to female. You could see the median age is 34 years old when it was studied but ranged from 5 to 87. The total erythrocyte porphyrin levels -- this is one of the novel findings from their study at least -- males tend to be higher compared to females.

The mean age of diagnosis is -- the mean age of onset is one year. However, notice the mean age of diagnosis is 12 years, indicating that for many of these patients, the condition would go unrecognized or undiagnosed for at least 11 years on the average. I think this is about the experience, I'm certain, of many of you.

Median time to the onset of symptoms, meaning of the burning, stinging sensation after sun exposure in this study -- about 20 minutes. The onset of redness and swelling is about six hours. So it starts with burning and stinging sensation, and then a few hours later, development of the redness, development of the swelling. I'm sure this is very,

very familiar to all of you.

The conditions -- that is the redness and the swelling -- would resolve without further exposure to the sun in about three days or so at least in this particular study. Again, I'm certain this is quite familiar to all of you from personal experience.

The other part that is highlighted in this particular study was the priming, which is essentially the condition would get worse, would be more noticeable following sun exposure. This is a term that Maureen Poh, actually, coined in the late '80s or so. You could see a good number of patients, 85 percent of the patients, had this priming phenomenon.

The second part that is known to, I'm certain, to all of you is that the absence of protection by window glass. You know that when you're driving in the car even with the window glass pulled up, you still can get the eruption. Ninety-two percent of the patients indicated that is indeed the case.

I just want to highlight and explain why that is the case. This is penetration of light

through UV and window glass. Let me just go over this a little bit slowly on this part here because it's a new concept probably for many of you.

But this is the wavelength of ultraviolet light in visible light coming from the sun -- shortest wavelength, longest wavelength. By convention, those wavelengths are divided into so-called ultraviolet lights and then visible light. Visible light is the one that we use for general illumination purposes. Ultraviolet light is the one that's responsible for sunburn and tanning reaction on the skin.

You could see that this is a study that we conducted with a glass manufacturer in Detroit. They make a lot of automobile glass. And you could see this is the transmission, meaning the higher the curve, the more light would get through that particular glass.

You could see for all types of glass there is no transmission below 320 nanometers, which is the sunburn spectrum. That is the reason it is very, very difficult for anybody to get sunburned from window glass filtered sunlight because all the sunburn

spectrum pretty much is filtered out by window glass.

But for the purposes of this discussion, the important part is that if one looks at the 400 nanometers, this is the cutoff between UV light and visible light. Again, visible light is the one that we use for general illumination purposes.

You could see for all types of glass there is very significant transmission of visible light because for visible light to be blocked by glass, the glass would have to be opaque. You know, you cannot see through the glass. Clearly, that is not the purpose of glass.

And then the important part, however -- many of you know -- the action spectrum of photosensitivity by porphyria is in the 400- to 410-nanometer range. This is right above the cutoff for visible light. That is the reason that glass doesn't protect against the development of photosensitivity in porphyria.

Other findings from this study -- exacerbation by wind; no family history of photosensitivity in about 58 percent of the patients; and patients also developed chronic -- that is,

longstanding -- skin lesions. Eighty percent of the patients have longstanding skin lesions. I'm sure, again, this is very familiar to all of you through personal experience.

I want to show you some of the slides here. But there's a little scar here -- very, very subtle signs on this patient's skin. In fact, when I see patients with EPP with our trainees, you know, we really have to ask them to pay particular attention because even, I mean, unless one is trained to specifically look for it, it can be missed even by dermatologists. And I think that's one of the reasons that the diagnosis sometimes is quite delayed.

This is another patient who developed -- you can see a little scarring just on the nose bridge there. And clearly, this is another one that is more noticeable, the pebbling of the knuckles as well as of the fingers here. Again, unless one is specifically trained for it, one can miss that -- and then another patient with similar type of changes that is even more noticeable. And then with a lot of sun exposure, there is sometimes some bleeding underneath the skin.

Red and blue marks can occur.

And the last picture is a picture that I am going to show from my colleague in Japan. In Japan, there is -- I'm sorry that the projection doesn't come out well. But this is a patient with EPP given -- a picture given to me by Dr. Georgia Kamerai (ph) to show that this is a patient with EPP.

She went on a school trip, sitting in a bus, getting sunlight through window glass-filtered sunlight for quite a few hours. You could see very significant photosensitivity reaction. Notice also that this is quite typical. The lower lip is more involved compared to the upper lip because, if you think about how the sun hits the face, lower lip always is more involved compared to the upper lip.

Coming back to the EPP in the UK study, symptoms change little with age, improve during pregnancy probably because of the hormonal changes. Twenty-eight percent were taking beta-carotene, and 56 percent had taken it, reflecting that there has been little options for the treatment of EPP. That's the reason I think this meeting is very, very important

for all of us to see what more than we can do for this group of patients. And most patients use protective clothing and a sunscreen. I explain to you already that protective sunscreen doesn't protect well.

And I'm just going to go over quickly because the red light is flashing here that we have the -- this is the UV light that I have just told you before. But I told you before that the action spectrum in EPP is in the visible light range.

We know sunscreen works very, very well against ultraviolet light, but no sunscreen works against visible light because for sunscreen to work against visible light, it has to be opaque. It is not going to be acceptable to most patients because you would be very, very noticeable. That's the reason sunscreen is not helpful, that all patients would have to use physical protection such as clothing.

Liver failure can occur in about 1 percent of the patients. Last -- two weeks ago, we have a case at Henry Ford where EPP patient needing liver transplant, which by itself presented a significant challenge because light in the operating room would

result in phototoxic dysentery (ph) in the abdomen as the abdomen is open for many, many hours during liver transplant. So we have to use yellow filter. That worked very well for the surgeons as well as for the patient, as importantly.

Gall stone -- this is 8 percent. Very importantly, quality of life is markedly impaired, with scores similar to those in severe dermatological diseases.

I'm preaching to the choir here. I'm sure you all recognized how much it had affected your daily activity -- not being able to go out. You have to use special clothing and so on and so forth. It does affect very significantly the quality of life.

And then most importantly, on the last slide here -- or the last bullet here, the total erythrocyte porphyrin, age of onset, time to onset of symptoms, none is a useful predictor for the impairment of quality of life among these patients.

So the bottom line is that EPP is a persistent, severely painful, and socially disabling disease with marked impact on quality of life.

I'll stop here. Thank you.

(Applause.)

UNIDENTIFIED FEMALE SPEAKER 1: Oh, sorry. I must be pushing the wrong button here.

(Side conversation.)

DR. EGGERS: So I'm going to come up and do my --

UNIDENTIFIED FEMALE SPEAKER 1: Okay.

DR. EGGERS: It's all an experiment, folks. So as to not waste a minute, I'm going to go and do my part of the -- to tell you about what the discussion format is going to be as soon as Dr. Teng's presentation is over.

We are going to talk about two topics in the next two hours, and that is the health effects of EPP and the impact that it has on daily life and then the current treatment approaches, your experiences, and your general perspectives on that.

This, as I said, is going to be a town hall-style discussion. And I want to say this might be one of the biggest groups of patients that we have tried to do this format with. So we are all going to have

to work together to move the conversation and keep it building on one another, but I think we can do it.

And I will take the difficult job. I am happy to have the job of keeping us on time and making sure that everyone who would like to speak, that we have a chance to get to as many of you as possible.

We have identified five people living with EPP to come up and present comments to really set the foundation for our facilitated discussion by giving a succinct story that we can build upon in the facilitated discussion.

So you know what? The panel discussion, why don't you come up -- as soon as Dr. Teng finishes her presentation, just come on up. We also -- so we'll hear each of the panel commenters, and we identified people who have a wide range of experiences, the best we could tell.

We will then build on what the panelists said in the facilitated discussion. So we may hear something that Monica says and will say let's hear -- are there other perspectives, other experiences, that are similar or different to Monica's and how you

describe your symptoms or your effects, for example.

Okay. Please, the best you can, stay on the topic that we are discussing. We are going to try to get -- we're going to be talking, first, the health impacts -- health effects and impacts and then the treatments.

When we get to the treatments, as Dr. Marcus said, we're not going to -- we will hear about specific treatments, but we don't want to focus too much on any one particular treatment. What we're looking for are the common experiences, what's meaningful to you about treatments in general. What do you look for, for meaningful benefits in a treatment?

And then we'll end it with if you could design the ideal treatment, what would it look like. What would its features be? How much improvement would you want to see?

So that is an overview of the discussion.

And if -- is Dr. Teng's slides available?

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

Okay. Then we will also -- Meghana, can we also for polling question clickers to be handed out?

While she's handing those out, we have a chance to participate to get your collective thinking, both here in person and on the web, through some polling questions. You'll use clickers and answer the questions that we bring up.

The purpose of -- these are not at all a scientific survey. What they do is they allow us to see what experiences are had by people in the room and on the web and where we might want to guide our discussion. So they're really a discussion aid, but they're very insightful for us.

And on the web, you can -- you'll have a chance to answer those polling questions as well. On the web, we are -- we know that -- first of all, we know that many people cannot travel today. It's inspiring to see how many of you could travel.

But for those of you who couldn't travel and you're participating on the web, please, your voice is as important as the voices in the room. Please type in your comments. Answer the questions. If I throw

out a follow-up question, type it in. We will sort out what that question was, and we'll get all the input in the right place. It'll all be incorporated and reviewed by us. So please participate if you're on the web.

Are we able to go to the polling question? Okay. Okay.

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. EGGERS: That's okay. What we could do is do this in the afternoon. We could do the overview of the treatment approaches.

DR. MARCUS: Sure. We could -- yeah.

DR. EGGERS: Would that work? One second. All right. I think they're getting it handled.

DR. MARCUS: Oh, okay. Yeah.

DR. EGGERS: So we've mentioned the part about an experiment bringing patients together for an expert workshop.

DR. MARCUS: Do you want me to speak a little bit?

DR. EGGERS: That would be great. Yes.

DR. MARCUS: While we're working on getting the slides up, I thought I would tell you a little bit more about the division and how we operate.

So we've got 42 people working in the Division of Dermatology and Dental Products. We have about 40 medical officers who review the scientific information that is provided to us for drug development programs. We have a group of toxicologists who review the supportive information that is used to support bringing products into human clinical trials for evaluation.

We have a team of project managers whose role it is to shepherd us all through the process, to serve as the interface between drug companies and the FDA and to run our meetings and document all discussions and agreements that we have with drug companies.

Are you ready? Okay. I can provide more information later.

DR. TENG: Thank you so much. Thank you for your patience. I'm sorry about the technical difficulty.

I'm coming from California, and I'm currently the director of Pediatric Dermatology at Stanford.

So here's a little three and a half year old little girl that I've been taking care of. When she came to me and she reported to have very similar photosensitivity, as Dr. Lim pointed out, at three years of age, you can already start to see these permanent scars on her face and her dorsal hands, despite not going outside and being very much sun protected at all times.

So when a patient is coming to us for porphyria or any photosensitive disorders, the first thing we do is, of course, to assess the erythrocyte porphyrin levels so that we understand their disease burden.

So in our rare disease clinic, we actually see patients of all ages, not just children, but adults as well, in addition that we also evaluate their extracutaneous disease burden by doing this laboratory testing that you're probably familiar with already.

And we look at their state of possible anemia, their iron load and to see if they're deficient and checking for their biliary and liver function and see if there's any abnormality has developed. And if there's any indication there might be extracutaneous manifestation of their biliary system or their liver, we go on to do some radio imaging study to make sure that they only have advanced disease.

So currently, you all know, there are challenges because there's no FDA approved treatment of this condition. And even for specific skin toxicity, we don't have a great treatment. So I'm going to get into that in a little more detail.

From the point of supportive care, aside from providing the necessary supplement because these, you know, people stay indoors all the time -- and some people may develop, like, a vitamin D and calcium deficiency. So the supplementation might be important, and immunization to protect their liver function is also important.

So the list underneath here is what we do

for surveillance. Every so often, we check for their liver function and other laboratory tests appropriate. Currently, in the United States, one of the biggest challenges for clinicians is there are very limited labs that provide adequate, consistent testing results.

And sometimes if I need to know a good -- give me a good profile, look at the urine, look at their serum, I have to send labs to several different locations. So not everyone, especially that even for providers who work with a genetic disease, if you're not familiar with this condition -- and sometimes we can't get the adequate testing results or surveillance results that you provide the adequate care that we needed. That's one of the challenge.

And the other thing that Dr. Lim has already alluded to is to identify precipitating factors, of course, in order to provide protection for patients. In a lot of people, it's a very severe disease. Oftentimes, they have significant pain.

And I've been taking care of a teenagers at 12 years old. At 10 years of age, they already have

lots of pain. Being indoors, they probably start to lose bone density as well very early on. They have the pain in their ankle when they're walking, and they are frequently on some of the pain medications. To address the danger of chronic use and addiction is also important. So that's kind of the supportive aspect of management.

So going to a little more specific management about EPP, we all heard about beta-carotene. As you know, a lot of people are taking it. It's not a great supplement. It's one of the natural substances that have been used frequently. But as you can see from the spectrum on your right, upper-hand corner, this is an absorption peak, you know, where and to what wavelength beta-carotene absorbs in most light.

And the PPI access stands for the protoporphyrin and to the two peaks not to completely overlap. And therefore, the beta-carotene can serve a very good function as a photo-protective rescue agent to quench the formation of those free radicals that cause the skin damages and also take a long time to

work.

And this is one of the references that Dr. Lim has already showed you, that in the UK study, it showed that lots of people using it, but the discontinue rate is very, very high. And that tells you it does not work great. And here's another list of the natural products that people have used, but none of these agents have randomized, double-blind clinical trials.

So you know, prior to some of the medical -- more specific medical therapy was developed, we really emphasized the physical protection from the skin standpoint. So we talk to patients about tinted windows and wear sun protective clothing, using wide-spectrum UVA and UVB protection sunscreens, sunblock. Use something at least, you know, SPF above 30 or as high as possible.

And for the OR cases that we just heard, those yellow glass filter over the operating room lighting is very, very important and not just for an open, you know, abdominal large surgery, but also for small, elective procedures. And that kind of a

protective measures are also very important.

Another treatment has been used. But again, there's no randomized study as the phototherapy, and the hypothesis is that it may increase the epidermal thickness in the melanin production of the skin, therefore protect the skin to a certain extent.

So the alfamelanotide -- and now I'm going to be a little more specific in medical treatments -- many of you have heard is a very exciting peptide hormone as depicted on the right, upper-hand corner of this slide.

The right lower panel is a schematic -- a simple schematic diagram of how the skin cells interact with each other. The keratinocyte side is that rectangular one, and the melanocyte is the one look like a spider with the dendrides (ph).

So as you can see that they are very -- they interact very intimately with each other because the melanocytes make mature melanin and passes it on to the keratinocyte to provide this uniform pigmentation on your skin and give people the protection.

Only 1 of every 10 cells on the skin

actually make -- is -- you know, have these little factories that are making melanin to protect the skin.

The alfamelanotide was initially discovered and especially as a clinical application use in the United States, but our European colleagues picked it up very quickly in the early 2000s. And it was used in Italy first, and it got approved in Italy in 2010. And then subsequently, several other European countries have also approved its use.

The Phase II and Phase III clinical trial has already been completed in Europe, so there are different phases of drug development and to evaluate the safety and toxicity. So that's why these drug developments are divided into different phases.

But it was first completed in Europe. And then subsequently, a similar study was conducted in United States, and it was recently published in the New England Journal of Medicine.

And you can see that all the patients that got recruited to study are above 18 years of age. None of them have any liver abnormalities. The U.S. study is slightly bigger than the scale of the

European study, but it's a little bit shorter. The U.S. study is six months, and the European study is about nine months.

And what they did was putting a small implant into the subcutaneous fat right above the iliac crest. There was a 14-gauge little catheter and then push it into the subcutaneous fat. The way that -- the reason that it has to be delivered that way is because the short half-life and the instability of this small peptide hormone on the skin. Therefore, it has to be implanted as a slow release to mimic the natural physiological state.

And so the clinical endpoint is very straightforward to look at, you know, the patients' pain-free time under the sun, to look at the phototoxic reaction -- you know, how many hours of significant pain that they have when they're exposed to sunlight during the study period and what their quality of life are like.

So I made the data very simple. Just the red letter -- numbers here highlighted was the treatment group. And the numbers on the left side and

the right side are a little different because the two clinical trials were not conducted at the same time, but it showed very similar results.

The pain-free time, that's the PFT, and it's on first row. And it show that with the treatment it does improve and also that patients can tolerate the lighting on the back of their hands and the back much, much better. And that was highlighted on the second -- in the middle part of the slide. And their quality of life score improved.

So what is the limitation of alfamelanotide? You know, first is that it's a relatively invasive way to deliver the drug. It's not as convenient as taking a pill or putting on a cream, and it does not provide any visceral organ protection because it binds directly to the melanocyte on the skin. And so it provides no liver protection. And we currently don't have any safety data in children and how safe it is in long-term use.

And the other question is that if we use this and the skin gets a little tan and it gives people more protection, will they spend more time in

the sunlight. Will they -- will it change their behavior in -- under the sun? And what is the implication in terms of how vigilant we need to continue to do the extracutaneous surveillance? So those are all questionable.

And the reason that alfamelanotide doesn't protect the liver is -- it's because the extra -- the PPIX, the protoporphyrin regulate the bile acids. We know -- we all know the bile acid in your biliary system gets rid of the extra lipids so that you don't form a gallstone and cause further damage to the liver. But the porphyrin causes -- there's a disruption, and that leads to causing congitis (ph) and biliary cell death in about 9 to 10 percent of the cases.

This is a very small case study we just published, and I want to point it out is that, you know, I'm a relatively newcomer to this particular genetic disorder, even though I take care of many patients with various different genetic disorder.

So about three years ago when a teenager girl came to me with excruciating pain and has to be

hospitalized every few months -- and I was a little appalled that there's no solution and no treatment except giving her pain medication. So I looked into the literature in more detail and noticed that cimetidine has been used for many years for two other subtypes of treating porphyria -- PCT and AIP.

So -- and I thought the cimetidine, or Tagamet, is a very safe medication. It's been used in pediatric patients for years, for decades. So it was approved by FDA in the '70s, and now it's an over-the-counter medication. So I thought, you know, no harm to try.

It's been three years, and all our three pediatric patients have done very well. They tolerate the treatment very well, and the pain and the photosensitivity has improved the first month they were on the medication.

And you know, the first patient that came to me -- and I live in a very sunny, northern part of the California. And the family bought a pool, and she sits outside and played by the pool in the summer with her peers. And so it's quite an amazing, very

rewarding experience for us.

Two of the children that initially had abnormal liver function tests and after they got on the medication became normal. Their liver function normalized very, very quickly. Here's some clinical photos we published, that the skin changes, as you can see on your left-hand side. It's before treatment, and the right-hand treatment is just within four weeks. And the skin texture has totally changed.

In the potential mechanism, there's no proof, but this is the hypothesis, that it is a new cimetidine inhibitor of the cytochrome P450, which is a Hem-containing enzyme. And you know, Dr. Lim has shown you the biosynthesis pathway, and it synthesize -- it inhibits the very first enzyme of this biosynthetic pathway.

So it's like, you know, if you have -- there's a drainage problem there, the metabolic toxic metabolite can get accumulated. If you just put a plug, you know, on the surface, eventually, the sink is going to overflow. So we have to stop the flow somewhere. And cimetidine may. It's, again, a

hypothesis. It may serve that function, but we don't know yet.

So another really interesting thing that I just want to share is that the patients that were on the treatment, they were also very active in disease group, that they have a blog on the porphyria website. It was the rest of the world.

And since then, we've received quite overwhelming amount of responses from Iceland, South Africa, everywhere you can imagine in the world. So I think that, you know -- again, I do run a large porphyria center. And perhaps this is something that we can consider and look into and see what the mechanism is. And nowadays -- in this day and age, there's so much development in understanding the genetics, the molecular biology, the gene expression profile of the different genetic diseases.

And perhaps this is something that will serve as a platform to teach us, you know, how we can discover other treatment options for porphyria. You know, not long ago, we didn't have any good treatment. For instance, infantile hemangioma -- we didn't have a

good treatment for tumors (ph) that grows (ph) in many of the congenital hereditary diseases.

And then soon we discovered by repurposing some of the drugs that are already on the market -- you know, beta blocker or other transplant medications. Now we're discovering new treatment, and we're repurposing these drugs to the market.

Each new drug that's developed that adds to -- estimated about $20 billion now. And if we can repurpose some of these new treat -- you know, these old drugs for new purpose, that would be pretty amazing.

And for liver transplant patient, another thing is that bone marrow transplant usually is recommended, right, so that they don't go into liver failure again. And so you know, there's a great need to discover new treatment to protect the organ that they are transplanted.

The last point I want to make, you know, about the drug discovery and think out of the box is that porphyria is not one disease. It's genetically very, very diverse.

I just listed three conditions that are going to lower the ferrochelatase to less than 35 percent but could lead to very similar clinical manifestations in both the skin as well as the liver. So you know, this is not one disease.

If we can, you know, figure out the way to address each population differently using a personalized approach, that would be very, very important.

So I'm going to stop right here. Sorry about the delay.

(Applause.)

DR. EGGERS: Thank you very much for those presentations.

And now we're all going to take a deep breath. And we're going to start the patient and caregiver aspect to hear from you.

Can I have the panel commenters come up at this point and take your seat?

While they're doing that, I went over in a haphazard way some of the ground rules. Let me go through those a bit more systematically for our

discussion. We really encourage patients and caregivers to participate in this discussion.

Some of you are pretty far in the back. You're going to have to raise your hands pretty high. We will -- we have microphone runners who are looking out for you. I can't see everyone, but the mic runners will be coming to you.

When you speak, please state your name -- it can just be your first name -- so that we can have -- so that we know in our transcript who's saying what when we do our analysis. FDA is here to listen. We know you probably have many, many questions.

There is a time for question and answer at the end of the regulatory talks in the afternoon when the questions can be asked. At this point, I think it's best for FDA to stay in listening mode and answering -- and helping me to ask questions.

If you do have questions, please feel free to send them to us. There's going to be -- I'm going to show you the public docket in a minute. We want your questions. This just might not be the best forum to answer all of them at this point.

As I said, we'll focus on symptoms and treatment experiences. I don't think anyone signed up for open public comment, which means that we will -- we get to just take all that time if no one signs up for it. And we will make sure we get as much out of the facilitated discussion.

Views today are personal opinions, and they're very personal experiences that we're sharing today. Respect for one another is paramount. I know I'm speaking to the choir here, but we just want to make sure we have full respect.

And that means if you also -- if you need to leave, for example, because the lighting up here is too much, feel free to take your seat. Whatever you need to do to make yourself comfortable, please let us know how we can help.

Also, let us know how the meeting went today with the evaluation forms that were at the registration table, and maybe they're at your tables now.

As far as continuing the discussion or allowing others who weren't able to participate today

to join the conversation, we do have a public docket, which is our way of allowing for electronic comments to be submitted -- emails or typing into a form.

We'll keep this up over lunch, and these slides will all be available on our website. But you can go to regulations.gov and search for EPP, and you'll be able to see a Comment Now button. Please, if there's something that you didn't get to fully say today, comment there. We review all of those comments. If there's something I say hey, we don't have much time to discuss that further, please address that in the public comments. Please do. It's very helpful to us.

With that, I think we can start with a few polling questions to let us see who's here today.

And I'm going to ask everyone, since we have such a large group, please limit it to -- if you are a person living with EPP -- we'll use the term patient -- or if you are a caregiver speaking on behalf of a person living with EPP so that we don't have any double counting.

We're going to try these polling questions,

an easy one first, which is where do you live. You'll click A if it's within our metro area here in Washington, D.C., or B if you're outside of the Washington, D.C., metropolitan area.

Okay. Oh.

UNIDENTIFIED FEMALE SPEAKER: We're still waiting for …

DR. EGGERS: Okay. It's -- maybe the -- okay.

You guys, I'll say this is one of the highest participations in the polling, and maybe we're going to be testing the limits of all of our technologies today. Yes, it's not surprising. Thank you for traveling here. For those of you that deal with the Beltway every day, thank you. But …

So this question doesn't make much sense anymore. But have you been diagnosed with having EPP, or do you have a child who's been diagnosed? Let's skip this one -- that one.

Okay. What is your age or the age of your loved one? A, younger than 18? B, 18 to 29? C, 30 to 49? D, 50 to 69? Or E, 70 or greater?

Okay. A wide spectrum. We have a very nice pediatric participation here today, which is difficult for some of the meetings like this we've held. And a special thank you to you.

We're going to try as best we can to separate out adults versus pediatrics, but feel free to join in whenever in the conversation.

Do you identify as A, male; B, female; or C, other?

Okay. We have a nice mix here today.

At what age did you first notice symptoms related to EPP? A, younger than five? B, 5 to 12? C, 13 to 17? D, 18 to 29? E, 30 to 49? F, 50 to 69? Or G, 70 or better?

Okay. Okay. Younger than five. Okay. That's pretty lopsided on our chart.

Do we have -- is the web the same or different?

MR. THOMPSON: It's the same on the web.

DR. EGGERS: Okay. At what age were you first diagnosed with EPP? And it's the same choices.

And if you're sitting up here, you can put

this on the screen right in front of you. Okay.

Now there's more of a range. This demonstrates -- illustrates the challenges that many of you may have faced in diagnosis. We won't be able to delve into that as a topic as much today, but it does allow us to capture that there might have been a range in the -- in your -- on the extent to which -- the time it took for a diagnosis to occur. On the web, is it about --

MR. THOMPSON: Very similar results.

DR. EGGERS: Similar. Thank you.

Okay. Now I think I can stop talking and will let our panelists go. Please push the red mic button. They've prepared a few minutes of comments each.

And we'll start with Monica. And bring it up as close as you can.

MS. FOLEY FLEEGEL: Okay. Thank you for allowing me the opportunity to speak to you today.

I've had symptoms of EPP since I was an infant. I am one of 5 in my family of 10 who have EPP. So my parents were able to quickly tell which

child could be in the sun or couldn't just by the way we cried, screamed, rubbed our hands and face after being in the sun for a few minutes.

The extreme pain is the worst symptom for me. The pain can be excruciating, and I'm unable to sleep for several days during a bad reaction. So trying to work, get groceries, do things around the house or even focus on conversations is almost impossible.

I've been asked to describe the pain, and I liken it to taking your hand and putting it on top of a broiler. The pain comes from deep with inside, but my skin tingles in a painful way. So I don't like anything touching it during a reaction. Usually, after the two to three days of severe pain, I am also painfully sensitive to cold temperatures for about two to three more days.

The most important activity I miss out on is family time outdoors. My daughter is now almost 20 years old, and I'm -- I don't want to cry. And I missed out on many activities with her from something simple as walking her to the park to play or helping

her move in her college dorm last year. I remember watching my husband and her leave for a day at Disney World and crying for hours after they left without me.

When she started in Kindergarten, I worried about all of the school events that would be held outdoors that I would miss. And there were so, so many over the years.

The other activity that is important to me but affected by my EPP is work. I work in human resources at Mayo Clinic, and for years I've had a position that required me to drive to different hospitals and locations several times a week.

To avoid the sun, I would leave hours before the meeting started and even walking those two blocks to my car in the summer was hard because I'd pray that no employees would stop me to ask their usual human resources questions. And then I'd be stuck in the parking lot in the sun.

Mayo Clinic has allowed to step down from my HR director role last year, so I now telework and don't have to worry about the drive I used to. I get many sun reactions a year -- excuse me. And as soon

as the pain, burning, and tingling starts after a few minutes in the sun, I quickly seek shelter. So my reactions last typically one to two days.

I just decided the pain isn't worth it, and I end up missing out on lots of outdoor time with my family and friends. I think out of the five in my family with EPP, we've all managed the disease a little differently. And some are willing to take more risks, but I tend to be the one to play it safe.

I typically do get a prescription for pain pills every spring. So if I do have a sudden reaction, I have something ready for the first one of the summer. The pain pills only help take the edge off the pain if I have a reaction. So the only way for me to totally avoid the pain is to completely limit the amount of time I'm in the sun.

Spring always seems worse for me. I'm not sure why, but I think it's because I get excited about warmer weather and I take more risks. And then I pay for it with a sun reaction.

I do wear UV protection clothing like gloves, hats, bandanas, long sleeves. I never, never

have had my feet exposed to the sun. So no matter what the weather, I always wear shoes and socks. The only other way besides protective clothing that I know of to manage the disease is to completely stay out of the sun and outdoor -- and stay indoors.

I did participate in the Scenesse trial last -- a couple years ago, and it was absolutely lifechanging for me. The first day, I sat out in the sun for 20 minutes. And I remember looking up at the sun and feeling its warmth on me. And I remember it felt almost therapeutic.

It was amazing to go for walks with my family, sit outside on the deck when friends came to visit, to not wear gloves every time I was in the car or walking to and from buildings. All of it was wonderful.

I also did a few trips during that time. And after 25 years of visiting my husband's family in Tampa, I actually joined them at the beach for an hour. I sat outside, and I even went canoeing for a little bit for the first time in my life. I also joined my girlfriends on their annual trip to New

Mexico, and I was able to hike with them for a couple hours in the sun.

But it was the little things that I loved. I loved waking up and seeing the sun shining in the house and knowing I wouldn't -- excuse me -- have to hide from it and schedule every activity based on the sun.

Even being out 30 to 60 minutes was lifechanging for me. And to be free from the pain would be the most meaningful improvement I could ask for, for a treatment. It was very, very hard to spend six months of my 56 years without pain and then to go right back to my old life with EPP when the trials ended.

DR. EGGERS: Thank you so much, Monica.

Now we'll have Madelyn.

MS. HARVARD: Hi. My name is Madelyn Harvard, and I'm 11 years old. I'm in 5th grade, and I live in Memphis, Tennessee, with my mom, dad, and my twin sister, who don't have EPP. I was diagnosed with EPP at four years old. My grandmother and her sister both have EPP, so I knew what was wrong from an early

age.

Because of porphyria, I can only tolerate about 10 minutes of direct sunlight before I get -- start to get a reaction. Once I get too much sun exposure, my skins gets -- starts to get tingly, and that is my sign I have had enough.

Next, I get very itchy, and this itching is very deep. I cannot scratch hard enough to make it stop. Then it starts to burn, feels like that part of my body is on fire. This burning feeling is under my skin, so it can't cool down.

These reactions can last up to five days. When I have a reaction, I can't sleep because the pain is so strong. It hurts so much. When I hurt -- when I put ice packs on my body and soaking cold baths, nothing helps the pain.

It is also hard for me to focus on my schoolwork when I am having a reaction because the pain is so strong. All I can think about is the pain and the burning.

Last summer, my family and I took a trip to Michigan. We spent about 10 minutes walking on a pier

to see Lake Michigan. That was all it took for my feet to get too much sun, and I ended up with a terrible reaction.

I spent the rest of the vacation indoors, soaking my feet in a bucket of ice water. The pain was so bad I couldn't get any sleep. The only way I could feel a little bit better was to keep my feet in ice water. I even had to ride home 13 hours with my feet in a cooler of water.

Since I have to stay out of the sun, I cannot play soccer, cannot go to the beach or play tennis on an outdoor court. My family and I can't even go to the park on a pretty, sunny day to have a picnic and play because of EPP. My twin sister gets to play outdoors, and I have to watch her from the window. I really wish I could spend time outside with her.

The main thing I can do to tolerate the sun is to cover up from head to toe. Just to go to recess, I put on a hat, sun sleeves, and golf gloves.

I like to run cross-country. And even though it is 100 degrees outside, I have to wear all

this gear just to run. Covering up is really the only way I can keep a reaction from happening. When I am outside for a longer time, I have to jump from shadow to shadow so I don't start hurting.

This past spring, I started doing light therapy. I spend about 30 seconds in a light booth three times a week. Getting to the doctor's office, doing my treatment, and coming home takes about two hours. The light therapy did increase the amount of sunlight I can handle, but it still isn't very much. I can walk across the parking lot without needing an umbrella for shade, but I can't go to recess without my sun gear.

I do think the light therapy is worth the effort for now, but it is not a good treatment forever. I need a treatment that will let me spend all day outside.

My mom read that cimetidine would help me spend more time outside, so she talked to my pediatrician and got it prescribed. I take it every day, but it doesn't help me spend any more time outside at all.

When I think about a perfect treatment for EPP, I would want it to let me spend all day outdoors without feeling any pain. It wouldn't take as much effort to get to as light therapy. I won't want to have to get it three times a week.

Since I was four and diagnosed with EPP, my life has been limited to what I can do outside. My hope is to have a treatment that will allow me to make up for what I missed out on. I need to have a future when I can be outside.

DR. EGGERS: Thank you so much, Madelyn. That was beautiful. Thank you.

And now we have Victor. And feel free to clap any time to show your encouragement.

(Applause.)

MR. MEJIAS: Exactly what they said, man. Is it hot in here, or is it just me?

All right. I'd like to thank the FDA for this meeting, the APF for everything they do, my EPP family. They're all here in support taking time out of their lives and from their family today to attend and the expense that we all went through.

My journey is similar to the others. I have EPP. We have the same stories, you know. They're a little different. Our tolerance may be different. The levels may be different.

But it's not a skin disease. EPP is a burn. It's not a sunburn. A sunburn attacks the skin. EPP burn is in the blood being toxified and sometimes causes the skin to show symptoms of phototoxicity.

My symptoms are physical pain -- the burning, the itching, the swelling, nerve aggravation. I don't know how to describe it. It's after I'm -- I call it bothered. I didn't know what to call it as a kid. And when I started getting bothered and started feeling the itching, my lip gets numb and I know it's time to go inside. And if I have too much exposure, after a while my nerves just start -- they start popping and shaking and tensing up. And I get very agitated, and you don't want no one to touch you. Sitting over there, I felt everybody's body heat. It's so much cooler right here. Truthfully, it is.

The emotional pain, the anger, the sadness, the depression, isolation, wanting to tear and rip

your skin off -- I don't know how to explain that either. It's just like you can't scratch deep enough, and the more you scratch, the more it hurts. You keep adding that pain. And it doesn't go away.

The feeling of wanting to die to get rid of the pain -- every day, 24 hours a day, 7 days a week, 365 days a year, I feel incomplete because I can't do my dreams, you know, and what I want to do, what I want to be, be with my family.

The symptoms I have impact my daily life, getting bothered. I step out into the sun. My skin starts to burn. It's kind of like putting your hand in boiling water. And while it's boiling, you add flame to that, a fire to it, and then just put your hand in the oven and get the heat.

When I'm bothered -- I lost my train of thought. When I get bothered, it just -- it's aggravating. It's -- I can't explain it.

Overexposure to sunlight on cloudy days -- just because the clouds are out, unless it's a massive thunderstorm, we still get the light that bothers us. So if you took your piece of paper and pretended those

lights were the sun, you could see the shadows. So even though we have our hats on, we're sitting in a car or under a tent, the light is still getting to us, especially through your windshield of your car. The reflection off the back of the car that's in front of you, it all adds up and all layers -- layers and layers and layers. And it's hard to recover from that.

It takes a long time. And because I work -- I choose to work every day, every day, walking to and from my car, to take out the garbage, to get the mail, to do whatever I have to do to help support my family, those layers just keep building.

Oh, and wearing the sun clothing -- when it's 90 degrees out, it's almost impossible. I mean, it's hot enough in here with the clothing on. Outside would be even worse. I get overheated. My body can't cool down.

Oh, and winter months are just as difficult for me as the summer months. For the winter months, I feel that -- I feel a little bit more protected because when I'm wearing my gear, gloves, hats, the

buff to cover my face and nose -- the winter months, the fall, you feel more protected.

I could wear a hoodie, and I'm not overheating. So I feel like I could do more. And it's cooler, so you don't feel that burn until you turn around and you get in your car. You go inside, and it's immediately you're just on fire.

The symptoms, they last for weeks. I already kind of said that already -- the driving to and from work, errands, grocery shopping, going to the bank, pumping gas, waiting for that car to move out of the way so you could have the shady gas pump --

(Laughter.)

MR. MEJIAS: -- picking up the kids from school, the stuff that I've missed, doctors' appointments, trying to get the doctors to stay open until 6:00 so I can go after work, you know, not go at noon.

I choose my jobs mostly on the direction of the sun, so I'm traveling with the sun on the opposite side of the car, jumping through shadows when you have to walk.

DR. EGGERS: Victor, you -- when we spoke, you told me a few very important things about what you look for in an ideal treatment, and I'd like to make sure that you get to those points as well.

MR. MEJIAS: Well, yeah. I joined the Phase II study trial. I didn't do it for me as much as I did it for the kids and for the kids to have a better future and what I missed out on. I couldn't -- I can't stand to think that they're going to have to go through what I missed. And that's why I did it.

I think the treatment helped. I was 42, I believe. It was very hard for my body and my mind to want to push myself into something that I knew was danger, that I knew would hurt. So I tried little bits at a time. It helped.

I got dark. I had the real drug. I got to spend some more time. The recovery was incredible. What normally would take 3 days or 12 hours or 24 hours seemed like it was cut in half or maybe even better.

I've had some work experiences that I've lost my job because of my EPP. I've had a job that I

told previously before I was hired, and they accommodated me. And then they changed accommodations because they changed the company structure. And I've lost my job.

The job I'm at now, I didn't tell them about it. I've been there for four years. I told them about it now because I was coming here, and they said, well, we'll do this, we'll do that, and we'll do this, you know, put the yellow filters. And they haven't done anything. The only thing I can do is try and help myself -- help protect myself.

I had one last thing. Am I out of time? Where did I put it? Oh, my God. I don't know where I put it.

DR. EGGERS: You know what? When we --

MR. MEJIAS: I might have lost it.

DR. EGGERS: It'll come up in the conversation, and raise your hand and make sure -- I'll make sure to come back to you.

MR. MEJIAS: Oh, I found it.

DR. EGGERS: You found it? Okay, great.

MR. MEJIAS: So the last but not least, I'd

like to ask the FDA for help. We need your help. We'd like to have a more normal life. The emotional pain of EPP can sometimes be worse than being on fire. EPP is the fire on the inside that no one sees, the emotional toll that no one believes.

Thank you.

(Applause.)

DR. EGGERS: Thank you, Victor.

And now we have Meghan.

MS. ROHN: My name is Meghan Rohn, and I was diagnosed with EPP when I was between two and three years old. Thank you for choosing me to be on the panel.

I've spent my entire life avoiding the sun, and the people in this room know that it is easier said than done. My worst symptoms are burning, itching, and super sensitive skin, so sensitive that even the air from a fan is extremely painful.

My life and that of my family's is completely different than it would if I were able to be in the sun. The curtains in our home are always closed. There are no outside activities during the

day -- no beach, no picnics, no washing the car or cutting the lawn, no camping, no theme parks.

Reflected sunlight from water, concrete, buildings or glass is as bad as direct sunlight. Now that I'm driving, I can't avoid the sun anymore. The only thing I can do is cover up with my hat, gloves, long sleeves, pants and special sunscreen that makes my face look completely white.

There is no medicine here in the U.S. that helps my disease. Once symptoms occur, nothing can ease the pain, burning or swelling except time. Sometimes I swell so much that my skin splits, and I have painful cracks and peeling of the skin.

Once sensitized by the sun, even artificial lights cause my skin to burn more, so I just sit in the dark for days, waiting for my reaction to go away. I walked to lunch at school with friends this past spring, and in 10 minutes I ended up in the emergency room and missed school for almost a week.

I realize that I'm only 16 and Scenesse is for adults. But I'm almost 17, and I'm so excited that when I turn 18 I might be able to have the

opportunity to live a normal life. I don't want myself or my family, both current and future, to miss out on opportunities like Disney or even Little League baseball or riding a bike around the block or playing in the backyard.

These are the things my family has sacrificed in order to make me feel included and not a burden to them. I want to choose a profession based on what I'm really interested in as opposed to what the sun will allow. And I want to be able to drive a car with the windows down or even the top down. I want to be able to actually go to the pool in the daylight.

DR. EGGERS: Thank you very much, Meghan.

(Applause.)

DR. EGGERS: Thank you.

Are you okay, Kerry? And now we have Kerry. Good luck.

MS. WILES: Just a second.

I was diagnosed at the age of three. My mother figured it out when I would run from shade tree to shade tree when we would go on walks. I had an

older, third cousin that had been diagnosed previously, and so we knew it was in the family. It was easier for me to be diagnosed.

I'm sure you're going to hear stories today, horrific stories, that the amazing people in this room have endured just to get a diagnosis, but I was a lucky one. And they knew very early what it was.

So I had a very loving and supportive family. My parents did everything they could to protect me. They put a roof over my sandbox. They created amazing opportunities for me to play indoors.

But while I had that loving support at home, the taunting and teasing of being a different child, the child that was different from other kids and teachers, was painful. And I hear their stories, and I see these little kids. That's triggering. That triggers trauma for us because, while I blocked out a lot of that because I don't want to have to think about the pain as a child, it was horrific.

I had a fifth grade teacher who made me -- because I couldn't go on an outdoor field trip, an all-day outdoor field trip -- he didn't believe me or

my parents and made me sit at home. And I had to write a five-page essay that took three days because I was 11 -- five-page essay to write because I couldn't physically go out and be in the sun. So the trauma from childhood, I've really tried to not process and think about anymore because I wouldn't be able to talk if I thought about it.

Throughout my life, I've worked really hard to manage this disease and avoidance. And while all of you -- we sit here. And I'm sorry. But this computer screen -- I appreciate us being able to sit back there because this is very bright.

I'm in a reaction. I drove. I was in a car for two hours yesterday trying to get from the airport to the hotel. And I was very -- I was in a lot of pain last night. I'm still in reaction today, and this is very bright. Sitting with this screen in my face, I'm in pain. But it is worth it because I am humbled to be a voice of all the amazing people here.

When I go into the sun, I wear sunscreen, jackets, socks, shoes, everything everybody up here has talked about. But even with all that, I still had

horrific reactions.

A year ago, I had a really bad reaction that lasted seven days. I'm a professional. I'm a mental health and substance abuse therapist. I work indoors because I didn't get to choose to work outdoors. But for four days, I couldn't sleep. I couldn't wash my body. I couldn't leave my house. I couldn't have lights on. I couldn't have my children give me a hug. I could not let anybody touch me. Imagine telling your children that they can't touch you.

Once that exposure happens, my skin gets so sensitive that I can't even have air moving. I think Meghan talked about wind or an air conditioner. Last night in my hotel room, I tried to sit at my desk and eat dinner, and the air conditioner was right beside it. I'm in reaction. I couldn't be anywhere near it. My skin crawls to the point I want to rip it off like Victor said.

Over the last several years, I've noticed that my symptoms are getting worse. I continue to be more and more sensitive. Once I have exposure, I'm less tolerant to computer screens, to lights, to

overhead lights. That's not stuff that used to bother me.

I'm not able to do my job. A big part of my work is on the -- I work a lot on the computer. I'm in meetings all the time, and if I'm in reaction, the light -- I am so sensitive I can't go to meetings. I can't go to work.

Because my symptoms are getting worse, I talked to my doctor about cimetidine, and I started that early this summer, late spring. And I have not had any noticeable improvements. It's not helped me, from what I can tell.

So I'm not sure if my current regimen of covering up and avoiding the sun controls my condition, but I can tell you that it helps me not have frequent reactions. But at what cost? The quality of my life as well as the lives of my family suffer.

Thank you.

(Applause.)

MS. WILES: My kids are in activities. They love to be outside. They don't have EPP, so they play

softball and soccer and baseball and cross-country. And if -- I miss all -- most of their events -- 75 -- at least 75 percent of their events. And if I do go, I have to cover up to the point that I'm embarrassing to them.

Imagine staying home for son's -- your three-year-old's first soccer game or missing your daughter's scoring the winning run in the championship game. We don't get to do typical family activities.

People comment if I'm covered up. Like Victor said, when it's 100 degrees outside, it's already hot. And then I'm in multiple layers of clothing, and strangers comment. They say things. Or I have an umbrella, and they're like it's not raining. They don't know, but they're -- people are very insensitive.

I don't get to do normal family activities because it puts my health at risk. I don't get to take my kids on bike rides or picnics at the park. We don't get to go swimming or going to zoo. We have the world-renowned zoo in my town in Omaha. I don't get to take my kids to the best zoo in the country. I

can't even take my dogs for a walk.

But the worst of all is the mental mind game that is EPP. The constant worry, fear, and planning is exhausting. How many of you in the room with EPP had to think about which side of the plane to sit on to come here or which side of the car you're going to ride on to come here?

We have to think and plan every minute of our lives. My husband isn't -- has to park the car a certain way to go get gas at a gas station. He takes me and drops me off at the front door of the grocery store and does all the housework and outside yard work himself.

It affects my friendships. I can't go on shopping trips. I love to shop. I can't go on shopping trips with my girlfriends or outdoor concerts. My friend has a lake house I can't go to. I don't get to attend work events that are mandated, but they do make accommodations for me.

I can't volunteer. As a therapist and a trained trauma therapist, I could go, and I could respond to natural disasters. But because of my EPP,

I can't go help when there's a hurricane. I can't go and do the things that I would love to be able to do. And I can't go and watch my beloved Nebraska Cornhuskers play football if my seat is not shaded. And that's important to me.

So I would say yeah, my regimen of covering up and avoiding the sun does help control my condition most of the time. But again, I ask. At what cost? Because the amount of suffering that goes into managing this is all-consuming.

Thank you.

(Applause.)

DR. EGGERS: I don't think I have to mention the courage it takes to sit up there and to be in the audience and listen as your children are speaking up there or your friends. Thank you very much for your -- for sharing comments that I think will really set the stage for our discussion now.

We are going to start with a show of hands. How many of you heard yourself in these comments that were up here? Yeah. It's -- you did exactly what we were hoping we would get out of this setting up of our

conversation.

We're now going to move and talk a little bit more in the details of things, starting with the health effects and the impacts. I mentioned we're going to try -- just raise your hand if you want to contribute to whatever the question was raised, and we'll try to get as many of you who want to share as possible.

Can everyone hear me okay? Okay. Anyone like Victor who finds it a little warm in here? Okay. If at any point you want to sit -- take a seat, or Victor, if you want to stay up here in the cool, feel free.

And please, I'll remind you. We don't have any scheduled breaks. So if you need to take a bio break, please do at any time.

We're going to start with a polling question. If you can get out your clickers, I think that all of you -- did anyone need a clicker? If you raise your hand.

Okay. Can we get some -- oh, no -- okay. Is that an extra one? We have more, I think. Just

for the -- so a patient or a caregiver who's speaking on behalf of a patient. Okay. Okay. Okay.

So of all the symptoms you experience because of EPP, which have the most significant impacts on your daily life? And you can choose up to the three. It might be a hard choice. A, skin redness or inflammation. B, itching. C, burning or stinging. D, pain or soreness that is other than burning or stinging. E, blisters or ulcers. F, swelling. G, skin thickening or scarring. H, lightening or darkening of the skin, so pigmentation changes. And I, other impacts not mentioned.

We focused here on the skin-related symptoms, recognizing that there are a number of other symptoms that are not skin-related, and we'll get into those.

Okay. So the burning or stinging was identified by most of you here. On the web?

MR. THOMPSON: Yeah, 96 percent burning or stinging, 60 percent for itching, and 35 or lower for the rest.

DR. EGGERS: Okay. We heard some very vivid

descriptions of the burning or stinging up here by you.

Does anyone else describe it in a different way? Can we get a few descriptions of what burning -- how you describe it to your friends or even your doctor?

And if you could state your name?

MS. BURTON: My name is Darlene. If you've ever worked with jalapenos or habanero peppers, you know. That burning gets on your hands, and there's nothing you can do about it until it wears off. Well, that burning is what I experience, and I find that it takes about five to seven days for it to wear off.

DR. EGGERS: Okay. And let me ask. Do you describe it as burning or stinging?

MS. BURTON: The burning.

DR. EGGERS: The burning.

MS. BURTON: Oh, and stinging, too, but the burning is -- just no one can touch you. You can barely touch yourself.

DR. EGGERS: Okay. Yeah, over here.

UNIDENTIFIED FEMALE SPEAKER 2: I'm from

Pennsylvania, and I explain it as, quite literally, a chemical burn from the inside out.

DR. EGGERS: Okay. Okay. A couple others? Right here.

MS. TAYLOR: I'm Nanelle. And also, it's like a chemical burn. And it's like a burn from the inside out --

DR. EGGERS: Okay.

MS. TAYLOR: -- as opposed to a surface.

DR. EGGERS: Okay. I just want to mention, as I'm about to walk into cameras here. If you haven't noticed, we do have some -- at least one person from -- that's not affiliated with FDA who is filming. If you have any questions about that or have any discomfort with that, please let us know. Otherwise, that person will be filming today's event.

Okay. So right here. Go ahead. Thank you.

UNIDENTIFIED MALE SPEAKER 1: So I hate to be the counterpoint here, but there is no word in the English language or any other language I know of to explain it. We call it burning. But in fact, I think somebody mentioned, cold is just as bad as heat.

The least variation in temperature just sends a wave of pain that nobody in this -- well, the few of us in the room have experienced.

(Laughter.)

UNIDENTIFIED MALE SPEAKER 1: There is no way to explain it. I've been doing this for over 60 years, and I can tell you. There aren't words.

DR. EGGERS: Does anyone use the word stinging to describe theirs more than, say, burning?

Back -- we have one back there. Okay. And we hope everyone feels comfortable to share. Maybe sometime you'll share a little bit later as you see this go on.

Then there was a comment over here. Then I think, Meghan, I had you move from -- we'll go back. Yeah. We love this challenge. Yeah, okay. Go ahead. It's not working. Hang on one second.

UNIDENTIFIED MALE SPEAKER 2: Hello.

DR. EGGERS: There we go.

UNIDENTIFIED MALE SPEAKER 2: I would describe it as almost like cutting yourself and being burnt at the same time.

DR. EGGERS: Okay.

UNIDENTIFIED MALE SPEAKER 2: That's my personal -- driving here, I always wear stuff. I might show you guys later, but just reflection got me yesterday. And that is --

DR. EGGERS: Go ahead.

UNINDENTIFIED MALE SPEAKER 2: And that right now is just like an underlying throbbing. And I know there's nothing I can do about it. Cold doesn't work. You try a cold cloth, and it just -- it dries your skin out. And then you've got dry skin, and it's really burning.

So it's just uncomfortable. And then if you get -- if I get direct sunlight for more than 20, 30 seconds, I'm going to have a full-out reaction. And that can last from five days to two weeks, depending how much I've gotten, and it's not pleasant.

DR. EGGERS: Okay. Thank you.

We're going to get into reactions in a little bit because we do want to know what makes a reaction time different from a better day.

How many -- can I have a show of hands? How

many of you are sitting here right now and you're at this meeting and you are in some sort of pain that you think -- that you would describe as pain -- burning, stinging or another kind of pain?

Okay. And how many of you are sitting here right now and you have some sort of itching sensation while you're sitting here? So it's constant. It's all the time.

Yes, go ahead, Victor. Put the mic on.

MR. MEJIAS: I printed -- my wife has them now. I sent it to the FDA. Pain level -- I made a pain level chart. And if anybody wants it, if anyone wants to read it, she can give you a copy if you want to see what our levels are like.

DR. EGGERS: Okay, great. Thank you very much, Victor.

A few comments on other types of pain that you wouldn't describe as burning or stinging -- so if you picked D above. And raise your hands high so we can see them.

MR. GARRETT: I'm David.

DR. EGGERS: Hi, David.

MR. GARRETT: I know that everybody answered that most, but I agree with -- Mike is my cousin. I agree with him. There's really no term for it. The only time that the stinging part is -- that's a great warning, and everybody in here knows it.

When you get trapped out there, you're in the sun. You can't escape it, and you're going to -- first thing you're going to feel is that little stinging that's on your skin that you know it's too late. You're out there too long, and it's going to get worse.

But the pain after that, it's -- like, maybe we should all get together and coin a word. But it's beyond that. It's not something you can describe. When I was a teenager and kind of in remission, I had a sunburn one time that was red as a lobster and didn't even bother me.

People could slap me, and it was like what -- you know, am I supposed to hurt with this? That's the realm you get into. And I don't know what the word would be, but that's it.

DR. EGGERS: I think you're just -- I think

you're all describing it well. That's why we wanted to hear from you today, is to learn from you about these descriptions.

That -- so if you look at the polling results -- and by -- I don't think I asked about the web, Graham. Are the web results similar or different in any way?

MR. THOMPSON: Yeah. We did go through. They're pretty similar.

DR. EGGERS: Okay. Were there any questions about the pain from my FDA colleagues, about the burning, stinging-type sensations or symptoms?

Okay. I want to ask about itching.

Oh, go ahead. I'm sorry. Go ahead, Kendall.

DR. MARCUS: Okay. I know there are some people in the audience here who've had this disease for decades now. And very few of you actually raised your hand about currently having burning or itching.

And I'm curious to know if after decades of having reactions and having episodes of stinging, itching, and burning, if you've developed chronic

symptoms -- if you have numbness in your hands, if you have constant, very mild tinging or if you have any numbness that's resulted from having this for decades.

DR. EGGERS: First, just a show of hands. Who would say yes to this? Okay. Can we take a few comments? Then it looks like about three or four of you -- a few comments to describe it.

UNIDENTIFIED FEMALE SPEAKER 3: I guess I never considered that it could be related to EPP. There's also numbness in my feet. I never thought it was related to that …

DR. EGGERS: Thank you. And then we'll take another one.

UNIDENTIFIED FEMALE SPEAKER 4: I'm 52, and I have to say the same thing. My hands and arms go numb all the time, and my feet do, too, like, when I'm walking. And so I didn't -- it could be related.

DR. MARCUS: Can I just ask you if -- I get the impression that most people cover their feet all of the time. Have you had reactions on your feet, or you're having numbness in your feet despite having kept them covered at all times?

UNIDENTIFIED FEMALE SPEAKER 4: My feet right now and at my age is my most sensitive part of my body.

DR. MARCUS: I'm sorry. I didn't catch that.

DR. EGGERS: One of the most sensitive parts of her body -- her feet.

UNIDENTIFIED FEMALE SPEAKER 4: My feet are my most sensitive part of my body at my age right now.

DR. MARCUS: And have you had sun exposure to your feet, or have you mostly kept your feet covered up? I get the sense everybody -- having your hands exposed is one of the most difficult -- is very difficult to overcome. But --

UNIDENTIFIED FEMALE SPEAKER 4: I keep my feet covered up for the most part, but it doesn't take very long for my feet to have a reaction if I'm even in the shade with reflected sun coming in.

DR. MARCUS: Thank you.

DR. EGGERS: Okay. So there were -- oh, one more.

UNIDENTIFIED FEMALE SPEAKER 3: Oh, well,

you had asked -- well -- yes, covering my feet up all the time and yes, that still has numbness on my feet as years go on.

DR. MARCUS: Can I just ask the same question about tingling? Because I've heard it from a few about numbness? But how about constant tingling?

DR. EGGERS: So if you're on the web and you experience that, please write in a comment to that. Or if you -- if there's others and they experience it and they're not here today, they can send something in to the docket.

Okay. No, of course.

There are many -- there are other symptoms that were identified by our panel members and identified by those of you who submitted comments in. And I just want to take a moment to say thank you to all of those who expressed interest in serving as a panel member and submitting comments in.

You don't know how valuable those are to us as we plan so we have a sense of what's going to be important to talk about today. So I wanted to thank you.

And in all the comments we've gotten up here, we heard about fatigue, difficulty -- and difficulty concentrating. So I was wondering if anyone would like to describe a little bit more about that and what you think triggers either of those two symptoms for you.

We have someone here.

UNIDENTIFIED MALE SPEAKER: (inaudible - off mic).

DR. EGGERS: Pardon me?

UNIDENTIFIED MALE SPEAKER: (inaudible - off mic).

(Laughter.)

MS. BURTON: I'm Nanelle. Is it working? Yes.

So it's the same experience, but -- and I know this is common with levels of pain. I'm a nurse. And when you assess pain, you know, some people express it different ways.

But I think for most of us, like, it's so intense that we just -- we turn inward. And so like with my children, you know, it's like I can't -- they

can't even look at me. It's like just leave me alone. You know, you're incredibly agitated. So you know, the anxiety is really high. And you just can't focus on anything. You just are, like, within yourself, like, trying to just endure the pain until, you know, the days, you know, two or three days and it, you know, subsides.

So yeah, you just cannot -- you cannot focus on anything, essentially. As far as I -- my experience goes, nothing -- nothing. I can't -- like she said, you can't bathe. I mean, you can't touch it. You can't.

You just sit there in as cool an environment as you can tolerate without making it hurt worse because it's cold, you know. So yeah, you just turn inward and, you know, kind of hunker down and suffer. So anyway, yeah.

DR. EGGERS: Thank you very much.

Right here.

MS. SILVEY: In my 20s, I kind of tried to pretend I didn't have this. And so I tortured myself, and I went to Disney with my family. And I don't

remember the last three days. We were there for five days, and I remember the first day really, really well.

And I, of course, had a reaction. I was covered -- didn't matter. And then I seemed to just not remember. They said oh, but we saw that big tree at the Animal Kingdom. And what I remember at Animal Kingdom is being in something that they said oh, you'll be completely covered. And it was an open trolley with a roof. That's not covering.

So I don't remember anything but getting on there. And I always equated it to I'm short. So I have a hat, and I can see you from about the waist down. So I know exactly what all the ground looks like, but I have no idea what anybody looks like.

So I just equated it to that. And I'm trying to plan another trip. And we were trying to talk about what we could do differently. And so that's how I figured out just recently that I didn't remember we had already done that.

So I have just complete memory loss of conversations, of being around my friends and family

after a reaction if it's bad enough.

DR. EGGERS: So again, we'll get into reaction. But first a show of hands -- and what was your name?

MS. SILVEY: Leslie.

DR. EGGERS: Leslie.

MS. SILVEY: I'm Leslie Silvey.

DR. EGGERS: Leslie.

How many of you here have experienced a similar situation of a reaction so bad that it has severely affected your ability to think or remember things? Okay. So I'm going to guess that's almost all hands. Okay. Thank you very much, Leslie.

Depression or anxiety?

Oh, go ahead. So we'll take one more. Go ahead. Go ahead.

UNIDENTIFIED FEMALE SPEAKER 5: It's working? Hello? I wanted to kind of go into the whole inability to focus once --

DR. EGGERS: Okay.

UNIDENTIFIED FEMALE SPEAKER 5: -- you have a reaction. I'm a teacher, and so whenever I go into

classrooms -- thankfully I'm a pushing (ph) type teacher, so I go into multiple classrooms.

When you are in reaction, your priority becomes safety. You're protecting yourself from the sunlight coming through the classroom window. You are noticing the reflection off the table, the door handles. That becomes what you're focusing on. It's a mental game of trying to keep yourself safe. So I can't focus on my work because I'm trying to not get burned worse.

And then also, fatigue is another issue that I'm always facing. I'm not quite sure what causes it. It could just be from the constant mental game. You're looking for your safest route. What's the best way to get there? How can I keep myself safe while keeping my toddler safe who runs away quickly?

So just two things I definitely see that I experience.

DR. EGGERS: Okay. All right. Victor, quickly.

MR. MEJIAS: Because before I said I lost some jobs because of my disorder, I didn't tell this

job about it. So I've been there for four years, and I told them now to come to this meeting.

But for three years, every time the doorbell rang, I was afraid the boss was going to ask me to go out there and drive the forklift to pick up the delivery, knowing that I can't do it. And how would I tell him no?

DR. EGGERS: Mm-hmm. Mm-hmm. So we're getting into the anxiety impacts. How many of you would have put anxiety in your top three if we had that as a choice? Okay.

Depression. How many of you would have put depression up in your top three? Okay.

We've had a meeting in the past where someone distinguished between fear and anxiety because I made the mistake of saying do you have a lot of anxiety. And the person said to me, no, you don't get it.

We have fear because we know what's going to happen. I'm not anxious about what's happening. I know what's going to happen.

How many of you would say that that fear is

a constant impact to your daily life? Okay. Thank you.

We're going to have to keep moving on in the discussion. I just want to see. For the kids in the audience or the parents, the -- any -- I mean, we had two beautiful descriptions of the pediatric perspective. Anything about experiencing symptoms that is pretty striking and you want -- would like to share?

UNIDENTIFIED FEMALE SPEAKER 6: My child has had so much pain that she has had broken bones and not even realized it.

DR. EGGERS: Okay.

UNIDENTIFIED FEMALE SPEAKER 6: And there was another lady at this table that talked about walking around with broken bones -- high fevers -- 103, 104 fever -- before we knew how sick she was because of her tolerance of pain.

DR. EGGERS: Thank you.

Any symptoms that you want to delve into? Any more?

Roselyn?

MS. EPPS: Thank you. I'm interested if people want to share about the other impacts not mentioned.

DR. EGGERS: Okay. Were there any other symptoms that we haven't covered yet? Okay. We'll come up here, right there, and then these three up in the front.

UNIDENTIFIED MALE SPEAKER 3: Sure. I think the one thing that, you know, we touched on a little bit, we're talking a lot about physical symptoms. And we mentioned anxiety and depression briefly, but I think there's definitely something to be said for having learned fear and doubt from a very early age.

I'm not sure if there are any, you know, psychotherapists or psychiatrists in the room. But having very early fear of pain, I think that creates a pretty, like, indelible anxiety, at least for me. I can't speak for everybody, but -- and then also kind of on the depression, doubt side of things, at a very fundamental level being -- feeling less than everyone else in a very literal way of not being able to do things that pretty much everybody else can do.

So I think, for me, those two things have had just as much, if not more, of an impact on how I live life. And whether or not, you know, my anxiety and depression is completely a reflection of EPP, you know, it's probably not. But to say it's not a major factor I think would be a, you know, mistake.

DR. EGGERS: Okay. So I'm going to guess that most of you -- that Kerry's not the only one who's experienced an event like your school field trip.

Nods to resonate. Did that resonate with you, that experience?

Yes, Kristin?

KRISTIN: Hi there. My name is Kristin, and this is my son, Brady. And he's had EPP for -- eight years now we've been managing it. And it impacts every single thing we do in our life. But what I'm deeply concerned about is what we're talking about, what this is doing to his mind.

And this is hard even to say in front of him, but I see his personality changing before my eyes. The anxiety, the isolation, the loneliness, how

people treat him, how he's treating the world around him, it's changing. And I can see it. And that's really hard to manage as a parent.

DR. EGGERS: Thank you.

Do we have one more? We'll come right here in the center, please. Oh, okay. We'll do two more.

Go ahead.

UNIDENTIFIED FEMALE SPEAKER 7: Isolation, to go with that, it's the same thing. But it has long-term effects in terms of how you function as a family member. But as a working person, everybody wants to know why you're not participating, why you're on the outside. And then the fear sets in, and you have a -- and you just -- you know, how can you explain it? But isolation would be a word that would encompass a lot.

DR. EGGERS: Thank you very much.

And here.

MR. TURELL: My name's Andrew. I'm Mike's dad. Mike's 28 now, and Mike was actually diagnosed with EPP when he was about three.

Before that, we knew there was something

going on. We didn't know what it was. We went to many, many doctors. They couldn't give us any solutions. There was swelling and so on of his hands and feet and face. And they gave every explanation except EPP.

And what really set it off was an unfortunate day when -- we always encouraged him to go out as much as he could, covered up. We went, actually, to a water park. He had a mask on. He had gloves on. He had a full bodysuit on. He had socks on, but he went swimming into the pool. And we didn't know that his socks came off with the weight of the water.

And obviously, the sun came through and hit his feet. And that set off just an incredible reaction. And his feet swelled up, and he had what we saw, that quite horrifying picture of the young lady who had sat on the bus, and that his feet went all purple. And it appeared to us like the blood vessels had broken under his feet. And he cried for, like, 36 hours. It was terrible.

The only good thing that came out of it was,

finally, we took pictures, and we took him to the doctors. And finally, somebody saw what the reaction was and said we think he might have EPP, and he was tested. And that's what he had.

I'm happy to say, as far as I know, he has never had quite that a severe reaction since because we -- you know, I mean you're just so precautious for everything and everywhere you go that you'd never -- you know, as a parent want that to happen to your child again. It was traumatic for everybody.

But I guess what I was kind of interested in, and maybe the show of hands, whatever, like, who -- patients in the room who've had that kind of reaction, that severe -- as a severe reaction as that --

DR. EGGERS: Okay. Yeah.

MR. TURRELL: -- in the past because --

DR. EGGERS: I think --

MR. TURRELL: -- that's --

DR. EGGERS: Let me ask --

MR. TURRELL: -- it's horrifying --

DR. EGGERS: Let me build on your question.

MR. TURELL: As a parent, it's just -- it's heartbreaking.

DR. EGGERS: Mm-hmm. For how many -- think of -- I want you to define yourself what a severe reaction is for you. Let's get a sense of how frequent that is so we can have a sense in the room. Is this -- does this happen on at least a yearly basis? Okay. Okay. We have to start someplace. Okay.

What you would consider to be a severe reaction, one that's setting you back for some days as we've heard described, okay, is it once every summer? Okay. Or spring? Sorry. Okay.

UNIDENTIFIED FEMALE SPEAKER: Spring.

DR. EGGERS: Okay. Is it once a month? Okay.

Is it once a week? Yeah, okay. We've run out of days to recover. Okay. Thank you.

(Crosstalk.)

MR. MEJIAS: I think I've been bothered for the last five years. I don't think I've had a break.

DR. EGGERS: Okay. How many of you feel as

Victor does, that you haven't had a break in a very long time? Okay.

KRISTIN: Sorry.

DR. EGGERS: Go ahead.

KRISTIN: I think the main thing to point out is the reasons that there's not more reactions is because they avoid the sun.

DR. EGGERS: That's right.

KRISTIN: So they don't have that reaction.

(Applause.)

DR. EGGERS: Right. Thank you.

So you also have raised in here what we have identified as impacts. And we have another polling question for that, so we want to make sure we get to that one. This will tie into what I think some of the last comments were.

Which aspects of daily life are impacted the most by EPP? And you can choose up to three impacts. A, maintaining your physical health, so it can be your health, your managing your EPP or other health -- other aspects of your health.

B, ability to participate or perform at work

or school. C, ability to participate fully in extracurricular activities. D, ability to concentrate or focus. E, ability to fall asleep or stay asleep. F, intimacy or relationships. G, emotional wellbeing. Or H, another impact on daily life that's not mentioned.

(Crosstalk.)

(Laughter.)

DR. EGGERS: So if you can use -- all of them. So we're trying to look to see if you -- if we force you to say of these, which one is -- that you would consider is most significant to you, up to three.

Yeah. We're coming with the microphone.

UNIDENTIFIED FEMALE SPEAKER 8: (inaudible - off mic).

DR. EGGERS: Oh, we have the folks on the web, also.

UNIDENTIFIED FEMALE SPEAKER 8: Okay. What I want to say is I'm 66 years old. I wasn't diagnosed until I was 16, 1966 -- in 1966. I had a first reaction in 1952. So all of these things look all

well and good, but like I said. I'm 66.

I don't go to school. I'm maintaining my physical health. This all impacts everybody in this room, every one of those statements. I can't imagine a child going through what I went through from the age of two, in my first reaction, to when I was 16 when I was finally diagnosed at the University of Pennsylvania Clinical Research Department, that anybody would go through.

I felt like I was isolated. I didn't have anybody that knew what I was talking about. I had -- my family had to get a psychiatrist because a nurse told I was trying to get all the attention to myself and just -- and the gym teacher, too.

And so the psychiatrist said I would grow up to be an actor, you know. And yeah, they did not believe -- nobody believed in the community about what I had.

But getting back to these questions, every single one of those is very important. Relationships -- you know, I didn't go out or go with a relationship at school because I liked the football guy. But I

couldn't go to any of his games, you know. I liked, you know, to go out to go horseback riding. I couldn't go out in the daytime. And who wants to go with you if you want to go to a trail ride at night?

All of those things -- participation in everything and relationships. A boy doesn't want to date somebody that can't go to the beach, you know, can't go out and play or go watch and play baseball.

So every one of us in here -- I mean, I've dealt with it for a long time, and these little ones are the ones that I care about the most. I want to make sure that they don't have to go through what we went through.

(Applause.)

DR. EGGERS: Thank you very much.

You've made a strong point. And by the clapping, you have made an even stronger point that you agree with her. So -- well, let's just see if there are a few things that we haven't talked about today that we want to make sure to get across.

I think we've talked about the ability to perform or participate in work and fully in

extracurricular sports.

Let's go to -- there's a large -- 50 percent or other -- so just very briefly, let's get some of those others that you have mentioned that we don't have up on our list.

UNIDENTIFIED FEMALE SPEAKER 9: Hi. I'm -- I just want to run through some of these on behalf of my daughter. She's 10 years old, and some of these are very impactful, just like the previous lady stated. But some of them we have completely changed our lives so much that they -- so that to help with EPP so that they don't impact anymore -- for example, maintaining physical health.

Most kids my -- at 10 years old go outside on rollerblades or skateboards or play soccer, whatever. We realized that is not a possibility, so she does Taekwondo. Again, we've had to ask them to dim the lights in previous times. Sometimes she can't even do an indoor sport like Taekwondo because the swelling if she's had a reaction, even the swelling five days later, she can't, you know, be hitting her hands off targets.

Her skin is so much thinner than normal people's that just hitting her hand off targets without having had a reaction any time previously, she's not able to fully participate.

Ability to concentrate or perform at work or school -- she's an extremely smart kid. But the concentration and the focus is sometimes not there -- again, not always related directly to having too much exposure.

The reflected light seems to be a big part of it because she rarely, if ever, goes outside without covering top to bottom. But she still manages to get enough light so that she's very -- she almost has a different personality when she's about to have a reaction.

She's very angry. It's like her nerves are on end, and I can tell her personality is changing. So I know that she's reached her limit before she can even tell the precursors of tingling or itching or anything comes on. Her -- the personality switch is almost like the Hulk. Sorry, Olivia.

DR. EGGERS: Yeah.

UNIDENTIFIED FEMALE SPEAKER 9: But yeah, she becomes difficult to deal with. And you know, in that kind of mood, obviously, she can't go to school and be expected to focus or concentrate. So she missed a lot of school days last year, not because she was itchy or swollen or painful, but just because there's absolutely no point sending a kid who's angry and upset into a situation where she's not going to feel comfortable.

DR. EGGERS: Okay. Thank you.

UNIDENTIFIED FEMALE SPEAKER 9: She doesn't have very many good friends because not many people understand her. A few good friends that she has, we're very thankful for them.

And she is treated generally very well by people who see that she's covering up. And she doesn't, you know, get strange looks. But I really worry about the future, how that's going to be. She's in middle school now, so it's just going to get worse and worse. I can imagine when she's going to high school it's going to be worse.

I can imagine if she's missing more school.

I worry about the impact on her future of having to miss so much school right now. And 5th grade is not -- you know, she can make up that work, but how is that going to be?

She wants to be a marine biologist when she grows up. Is that a realistic goal for her to have? Do we actually have to choose her career goals based on this disease?

Everybody has touched somewhat on all of this today, but this is the worries of a 10-year-old girl's mom. And it just -- it sucks. I mean, sometimes -- thanks.

It really struck home with me today to hear all of you adults talking and how much you're missing out on your children's lives. And I think -- I don't have to miss on anything for her because we tailor her life so that it has the least impact as possible. But is that going to be what it's like in the future? You know, when she's a mom, is she going to be missing her kids going to their first day in Kindergarten and all those things?

We definitely need to figure something out

so that these kids -- there's 5 11-year-olds in the room today. I really hope by the time they're thinking of going to high school and college that it's not going to have the same impact as everyone else in the room. I'm sorry for taking so much time.

DR. EGGERS: Thank you very much. Thank you.

(Applause.)

DR. EGGERS: So Kendall has a few questions, a few follow-up questions.

DR. MARCUS: So I'm just going to ask questions until you stop me so that people can have time to speak.

But I'm really trying to -- I have an analytic mind, and I really need to break down a lot of your symptoms into -- I really need to quantify it and better get a sense of the quality of different impacts so that I can best understand what leads you to the -- it sounds like the endpoint of pain, there are many factors that go into experiencing pain. And I'm trying to break it down so that I understand how all of you who come -- who probably have a variety of

genetics that lead to the same endpoint of disease, how different things might impact.

So I know that you're all from a wide geographical location, and I have a number of questions about, basically, where you live in terms of the time of year. Are there better times of year when, you know, winter being less impactful than summer depending on where you live versus living in a climate that has constant -- a greater intensity of sun? So are there people --

DR. EGGERS: Wait. I'm --

DR. MARCUS: Yes.

DR. EGGERS: Can I just -- I have an idea for this.

DR. MARCUS: Okay.

DR. EGGERS: We are going to -- let's ask you to read through all your questions.

DR. MARCUS: Okay.

DR. EGGERS: And then we're going to type them up.

DR. MARCUS: Perfect. Okay.

DR. EGGERS: And this -- some of this stuff

is going to be perfect docket comment. We have an assignment for you. The division director would like you to answer these --

DR. MARCUS: Okay.

DR. EGGERS: -- particular questions. We can get to some of them today, but I'm looking at your list.

DR. MARCUS: Yes, yes.

DR. EGGERS: And it's longer than we're going to be here.

DR. MARCUS: Okay.

DR. EGGERS: So just read through them, and then we'll pick some to go through.

DR. MARCUS: Okay. So I've heard both that extremes of temperature can impact the amount of pain that you experience. And I would like to know if you go outside on a sunny, cold day, is that -- are you more likely to experience pain than on a sunny day where the temperature is 70. So I'd like to know about the extremes of hot and cold, how that impacts pain.

I would like to know about wind. If you go

outside on a windy day versus a not windy day, is that going to result in developing a reaction sooner?

Altitude, being up at 5,000 feet -- people -- a number of people have described skiing and still getting what sounds like wind burned where, really, the end result of everything that we're talking about is pain for you.

And so I'm trying to understand as -- I'm just explaining to you. I'm trying to understand how all of these different factors can impact how long it takes for you to develop pain.

Humidity -- dry heat versus humid heat. I certainly understand once you're in pain, water can even be painful. But I -- it just made me think of the question about does even humidity make a difference.

Type of clothing. I don't get any sense that the type of clothing that you wear impacts the amount of pain or how soon it might take for you to develop a pain reaction. But I just want to be thorough, and I'm asking that question.

And I think I've already gotten to the

question about time of year. So there's that question.

I have a question, really, about -- and you know, I get the sense that there are people who are risk takers. I mean, and this is true of everybody, regardless whether you have EPP or not. There are people who I would categorize as risk takers, and there are people who I would categorize as risk avoidant.

And so I would like to know, for people who are risk takers, if you experience more burns in general in order to have more experiences in your life and not be as limited as you would if you avoided painful reactions.

I guess I have to ask. Is having fewer reactions more important? Or if you're the type of person who pushes yourself to the limit, regardless of what that limit is, is it the number of reactions, or is it the duration of the pain once you get it?

Because I've heard -- and this is new for me, I think -- I haven't heard this before -- that some people who received treatment had a decrease in

the duration because I hear, in general, it takes about three days once you have a reaction to really recover to the point that you can function again.

But it -- I'd really like to know if it would be meaningful for people if they do have a reaction, if it's just one or two days.

DR. EGGERS: We can do this one. Let's do this one as a hands --

DR. MARCUS: Okay.

DR. EGGERS: -- because this is getting into what a meaningful benefit would be.

DR. MARCUS: Yes.

DR. EGGERS: So -- and you can explain more then in the docket comments. You can submit your comments.

So there were two choices. You want -- one choice is fewer reactions, or the second one is maybe a less severe reaction that you can recover in shorter time.

DR. MARCUS: Right, yes.

DR. EGGERS: So the two choices -- fewer reactions or --

MR. TURELL: I think it's three --

DR. EGGERS: Three choices? Okay.

MR. TURELL: -- because I think sometimes I have more severe reactions. Sorry.

My name's Andrew. I really think it is three, distinct --

DR. EGGERS: Okay.

MR. TURELL: -- variable, more severe reactions, which haven't lasted as long --

DR. EGGERS: Okay.

MR. TURELL: -- for whatever reason as more minor reactions that have persisted at a duller level for a longer period of time. So I really think we could split it into three, distinct factors.

DR. EGGERS: Okay. All right. Let's do a show of hands of those three. Your choices are fewer reactions, less painful severe reaction, or a reaction that lasts -- that you recover quicker, okay? So those are your three choices.

Raise your hand for -- oh, this is a hard.

(Crosstalk.)

(Laughter.)

DR. EGGERS: You're not -- okay. So the -- all right. So we can't -- all right.

(Crosstalk.)

DR. MARCUS: So I guess what I'm getting at is trying to -- it's not clear to me that you all are able to go outside with a stopwatch and really gauge that something's had an impact on your ability to stay in the sun other than you're out there until you get a tingling. Does that make sense?

UNIDENTIFIED MALE SPEAKER 4: Can I say something?

DR. EGGERS: Well, let's go to Kerry first.

MS. WILES: So I think one of the trickiest parts for me is this is a very unpredictable issue. There are days where I can maybe be outside for 10 minutes and the tingling happens and I know I got to get out of the sun.

And there are days just walking, literally, for 30 seconds to my mailbox and back I'm in reaction. It's unpredictable for us. Whether -- like you said, is it -- if I do this, is it going to be a long duration or a short duration? Is it really intense?

Is it not? It's not predictable for us. There's no stopwatch. I don't know what my tolerance is because every day's different.

DR. EGGERS: We have a hand raised back there.

MR. MOULEDOUX: Pierre Mouledoux from New Orleans.

I'm a realtor by trade. And I'm going to tell you I'm outdoors a whole lot. I'm in my truck. I had to change the law for window tinting in Louisiana. I'm the only guy in the state with a legal tinted windshield, and it really does vary.

It's not whether you go to show one property or you go to 40 properties in a day. It really does vary -- time of year, how long exposure. You just don't know. You know, did you consume enough water? Did you eat enough carbs that day?

You know, there's so many more things out there than do we want less reactions or we want a shorter reaction. We're talking about being able to lengthen our exposure. That's why we're here, you know.

If we can enjoy our life, we're only here once, you know. This is what it is. It doesn't really vary from the length of reactions to the duration. We want to be able to extend our lives, and then we can deal with that afterwards. That's kind of where we're looking.

DR. EGGERS: Go ahead, Kendall.

DR. MARCUS: Just to summarize what you're saying is it's, A, very unpredictable. But despite that, you are able -- and you described very well, I think, being able to sit outside for 30 to 60 minutes where you hadn't before.

So I guess that's a semi-quantitative measure in what is otherwise an unpredictable disease in terms of sun exposure. I mean, there -- I understand it's very unpredictable. But at the same time, you know, I hear about benefits that sound significant, that are, in a way, quantifiable because it's an activity that you couldn't do before.

And you can tell me the amount of time, but then trying to drill down further on smaller increments of time, it becomes very difficult. I

guess that's what I would summarize about what I'm hearing.

I guess I'm curious to hear a little bit more, and I understand that the answer may be I don't know, just as you've described about time in the sun. But you described severe short reactions versus less severe, longer reactions. And I anticipate your answer is going to be you have no way of -- you don't understand what will cause a severe shorter versus a less severe longer.

UNIDENTIFIED MALE SPEAKER 4: Thanks.

No, I'm happy to address that because I think there actually is a difference. I think we have been talking about reactions often as if they start at this minute of this day.

But what we forget is that we are always exposed to light and that the cumulative amount of light that you continue to be exposed to absolutely affects a reaction, that there's no singular start time.

So with a more mild reaction, you might try to continue to live your life, that if we stopped all

of our activities the second we started feeling any reaction, we would never leave the box in our room. But -- so what I think happens is that once we have a more severe reaction, we often pull back to a greater degree. And so then we might not resume activities until that reaction is completely stopped, when with a more mild reaction, we don't alter our lives to as great of a degree from our usual habits. And thus, it might continue for a longer period of time at a more moderate level.

DR. MARCUS: Okay. Thank you.

That's really helpful, and it sounds like what you do during a reaction can have as much an impact on the duration as what you've done before the reaction.

Thank you.

DR. EGGERS: All right. I'm just going to have to put my facilitator hat on. And looking at the time, we are -- we -- I don't -- we don't have any open public comment? Okay. So then we will -- and if there is someone for open public comment, we have the afternoon that we can do as well.

I'm -- we're going to borrow as much time as we can. So we're going to borrow the 15 minutes from the open public comment and keep this discussion going. And then we'll make another call at 12:45.

Please, if you have to use a restroom break, please go do so. I think the -- I think we all want to stay in here for a little bit longer to have this conversation. We're going to take that -- we're willing? Okay.

I have a few more questions, so I just want to know. You can -- we can -- you can go the way you want to go.

DR. MARCUS: Sorry. I guess this is as much a comment as it is a question. And I think one of the most striking things I heard this morning that I haven't heard before is a lady over here mentioned -- I believe it was your daughter broke a bone and didn't know because of her level of pain tolerance. Is that -- am I -- do I have that detail correct?

UNIDENTIFIED FEMALE SPEAKER 6: That's correct. Actually, she's had six broke (inaudible - off mic).

DR. EGGERS: Okay. Six -- so if you couldn't hear her, she's had six broken bones that have gone unnoticed for several days.

DR. MARCUS: That's quite remarkable to me, and that speaks to a level of pain and pain tolerance that we're not capturing on a pain scale. And I -- you know, I think about the pain -- the visual -- you know, we have what we call visual analog scales where you have a smiling face, you know, on one end and you have a crying face on the other end.

And I honestly believe that could not necessarily capture or distinguish between levels of pain from reactions if you're telling me that your child is breaking a bone and doesn't even know it.

So that is really, really important, I think, for all of us to understand when we are trying to distinguish a drug -- you know, when a treatment has an impact that we be able to design a pain scale where we can discern an impact on pain because I think that the other piece of information that I've heard, I think, when I -- we received some comments for this meeting or today, is that I think also to the

tolerance is that you don't know how bad it's been until you have relief from the pain.

And so when you're filling out a pain scale, you, yourself, I believe, may not even know that something's benefitting you because you're going from a 15 on a scale of 1 to 10 to a 10 on a scale of 1 to 10. And I see a lot of heads nodding in agreement. But --

DR. EGGERS: We can put in our list of questions for if you have a chance to do -- provide additional comments is your experience with doing those pain scales. And I think Victor and others have had that.

Dr. Teng?

DR. TENG: Can I just make a quick comment? I was wondering. Is it rather unusual to have a child with six broken bones at once? Pain is one issue. And the other thing that I mentioned briefly is that some of these kids with chronic diseases and whether from their chronic disease or just be indoor all the time and their bone density are not monitored adequately.

And therefore, they're very susceptible, and they're at risk for fracture and not just with EPP. We see it with many other skin diseases as well as a genetic condition, that some of the kids get severe, you know, loss, have a very severe loss of bone density by the time they're six or eight years of age and to the extent that they will tear bones.

So you know, I'm wondering. You know, pain is definitely an important issue, but there may be other systemic ramifications and manifestations, perhaps, that we should also take into consideration from the overall health of children.

DR. EGGERS: Thank you very much.

And Electra has a question.

DR. PAPADOPOULOS: Yes, I heard people describe their reactions as, you know, on a spectrum between mild and severe. And I wondered what -- whether there's a qualitative difference in how you would describe a milder reaction versus a severe. Or is it the same sensation, just a matter of intensity?

DR. EGGERS: So different sensations or the same?

We have a comment in the back.

MR. WILLIS: First, I wanted to say something about the broken bones. My son broke four bones last year, and I didn't even believe that he was injured because his pain tolerance was -- is so high that he showed no signs. He wasn't crying.

He was -- he said mom, I broke my bone. He said I think I broke my hand. I thought he was joking. Two days later, I took him to the doctor. He had three broken bones in his hand. And two months before that, he broke two bones in his wrists. And I wouldn't have believed it was broken, but it was.

And when it comes to the differences between reactions, when he was six, he wished for death. And that was his -- the worst reaction he ever had. And the other times, he just begs for ice packs. But -- so there is a big difference between a mild reaction and a major reaction. I mean, a six-year-old begging for you to kill him is not something that a mother wants to deal with.

DR. EGGERS: One more. Anyone else? Okay. Right there. Yeah.

SHAWN: Hi. My name is Shawn. I'm actually -- I have a little bit of a reaction in my face today from driving here yesterday, and I even wear this mask to drive. Worst reaction I ever had was similar to the one that was shown on the screen where my face looked like raw hamburger.

It -- I swelled, turned purple, the whole deal, and then it turned into just raw skin. And it was horrific, and it led to a lot of other, you know, health issues that I dealt with after that.

DR. EGGERS: Thank you.

DR. PAPADOPOULOS: And are there symptoms that you experience every day in between these reactions?

SHAWN: Are you asking me, specifically?

DR. PAPADOPOULOS: Yes, and for everybody.

SHAWN: Yes. So I think it's just a matter of how much exposure we're willing to accept. So I don't like feeling that way, so I wear gloves and mask and a big hat or a drape hat that covers me completely when I do activities outside or if I have to drive for any distance at all.

Generally, a hat and gloves covers me from building to car. But the tingling, the burning that everyone's described, those are my trigger points to know when I'm -- to get out of it.

DR. PAPADOPOULOS: And what about itching? Are -- do those symptoms occur in between as well?

SHAWN: Itching for me only occurs later, and so that's post-burning and then to get into the reaction. And then I have itching at that point.

DR. EGGERS: Go ahead.

UNIDENTIFIED FEMALE SPEAKER 10: I was going to speak to that question as well. It's kind of hard to answer the question, kind of like the other answers we had to give as far as the qualitative measures and if we have symptoms in between exposures.

But I guess I would say the symptoms we have, or for me personally, are only if I am willing to go near a window or outside again. So if I have to function, yes, I'm going to have the symptoms. If I can stay inside and close the drapes, no, I'm not going to have the symptoms.

So yeah, if I'm going to go to work or go

grocery shopping or bring the kids somewhere, I have to cover up. And I have the symptoms and too bad. You just go on with your life. And that's more of a mild thing.

If it gets worse -- and everybody around me usually knows when it is -- I just have to go hide. But it's kind of hard to answer the questions because you -- whether or not you have those symptoms is whether or not you want to work and be a mother and function. So yes, we have the symptoms all the time.

(Applause.)

DR. EGGERS: Julie?

DR. BEITZ: I just had a question about the therapeutic or non-therapeutic effects of water. We heard about soaking a limb in cold water. Do people find that useful as a way to get around their reaction or not?

DR. EGGERS: So if you find it useful, do a show of hands.

(Crosstalk.)

DR. EGGERS: It's not practical. Okay. So may be useful. Did someone -- I think we read a

comment that it actually -- it makes it worse. Anyone for whom water makes it worse -- cold water?

(Crosstalk.)

UNIDENTIFIED FEMALE SPEAKER: Initially, it feels better.

UNIDENTIFIED FEMALE SPEAKER: Right.

UNIDENTIFIED MALE SPEAKER: Yeah.

(Crosstalk.)

DR. EGGERS: So short term --

(Crosstalk.)

UNIDENTIFIED FEMALE SPEAKER 11: So basically, when you stick your hands in the water, the tingling and the burning tends to subside slightly. But then when you take them out, now they're dry because they've been in the water. They crack open. And that's when you see the reaction like you saw in her face.

So I have several scars on my face -- you're welcome to come and examine me -- from when I was younger. We would put cold packs of just water on -- just cloth, typically, on -- soft cloth that would be on my face. Well, that tended to dry me out.

While it was good at the moment and I would stop jerking, my parents couldn't figure out why later, you know, a day later, my skin cracked open. And it was like a pus almost that comes out of our skin.

DR. EGGERS: Okay. Thank you.

Okay. We had one. Yeah. Let's -- we'll go back here, and then we'll come to Madelyn.

UNIDENTIFIED MALE SPEAKER 5: I really want to make sure that everybody understands that, in terms of the burning, that there's a cumulative effect. And so what we have a is buildup of that pain. And any exposure once you're burned just exacerbates the pain that you feel.

And I just want to make sure that we understand that, you know, it's a sum total of the burning event that brings us about to the severity of the pain that we're describing here.

DR. EGGERS: All right. Now we'll go with Madelyn.

MS. HARVARD: To me, if you keep -- if you put your feet in water, you can -- like, if you have a

bad reaction, once you put it in there and if you take it out, it hurts a lot worse than when you started. So you have to keep it cold until the reaction stops, or else it hurts worse.

DR. EGGERS: And you described going 13 hours, I think, on the way home.

MS. HARVARD: Because I had --

DR. EGGERS: Anyone else had an experience like Madelyn? Yeah. Okay.

So I just want to do a little time check. We have a couple more -- we'll have a couple more time for the FDA questions. This is great that you have so many questions.

When we come back after -- we're going to stop at 12:45 for lunch, and we're going to actually ask you. They're going to still be setting up the lunch. We didn't want them to rustle and to disrupt our conversation. So lunch will be prepared about five minutes later. It will be ready.

When we come back for lunch, we have a couple -- we're going to go pretty briefly, but we're going to continue this dialogue and do a couple final

questions that we weren't able to address beforehand, even if it means cutting into the scientific component a little bit.

Okay. So we have five more minutes for a few more questions.

I think Jonathan had a question.

MR. GOLDSMITH: Yeah. Thanks. I just wanted to understand better about the use of clothing that you use for covering and how commonly it's used. And is it used every day by a certain number of people? Is it used episodically by everybody? I just don't have a feel for how commonly it's -- you know, that it's employed.

(Applause.)

UNIDENTIFIED MALE SPEAKER: Let's hear.

MICHAEL: I have a kind of approach where I live life, not live a disease. So I can't have sun for more than 20 seconds, or I'll start to have a reaction, any more than a minute.

And the problem with me is reflection. I cannot tell constantly where the sun is coming from. And by the time I feel it, it's too late.

So what you see here is what I wear every day, all day. I work outside. It's my own business. I don't know why I chose it, but I did, right?

(Laughter.)

MICHAEL: So I wear this all day, every day.

It gets hot. I get heatstroke sometimes. I -- if I want to go to the mall, I wear this until I get to the mall. You can imagine how people react, right? What are you, cold? I get that every day. Are you a terrorist? People just start doing this, right?

But I've tried just wearing hoods. You get reflection off the ground. You get it off clouds. You get it off everywhere. I've had cops. You get stopped. It's all -- you know, it's not practical.

So when you were asking what would I like out of a drug, I would like to be able to walk 10 feet to my car without having to put this on. I would like to be able to go to the park without having to put this on. My wife would like to have a baby. I cannot imagine. I have enough difficulty now traveling like this.

What's it going to be like if I child with me, right, just the reception, the trouble I'm going to have. This works for me. I -- like I said, I don't let this stop me from doing anything.

And coming down here, I drove 10 hours 2 days ago, and I rented a car. My car at home is tinted. You cannot see in. The front windshield is clear. You can barely see in. And the reason I wear this in the car is because the tint doesn't work. The tint is strictly so other people do not see me so I don't get bothered.

So I got a rental car to come down here. I didn't want to wear this. I'm paranoid about getting shot. I don't know.

(Laughter.)

MICHAEL: It's probably irrational, but I'm from Canada. And that's all you hear, right?

(Laughter.)

MICHAEL: So when I drove down, I drove down with a hood, my gloves, and a hat. And I just got reflection here and there, and I'm itching. I'm trying not to touch it because touching makes it

worse.

So you also asked about the seasons. For me, you think, oh, winter, not much sun. It's better. No, because now you have it coming off the ground and from the sky, and it's just brighter in general, I think.

Vegas, I was there in the spring. I found it worse. I don't know if it was just the ground is shinier, what it is. I was very, very cautious. And I took two weeks to recover when I got home. And I was -- well, I wore this, and it was -- if I was sitting in the shade, I thought I was okay -- probably the clouds. I don't know what it was, right?

So I'm basically hoping that I can live a somewhat normal life as far as not being judged on what I'm wearing. And that would be my dream. I don't know. Like I said, I don't let it stop me because I stay covered.

I do not take any risks. I'm a risk taker. I drive motorcycles. I drive dirt bikes. I broke my leg in three spots on a dirt bike. I stood up thinking I was all right, fell over. So you asked

about pain. That's pain. And I thought I could walk away. No. Right?

So it's -- I don't know. That's what I do. I think there's a few of us like that, and I think you also get a variance.

Some people can take -- like, I think some people said five minutes. Some people said 10 minutes. Myself, I've tried it. I'm telling you. Twenty seconds, and I'm toast. So why take the risk? Just wear that and hope I don't get shot.

DR. EGGERS: What's your name?

MICHAEL: Michael.

DR. EGGERS: Michael. Thank you, Michael.

DR. MARCUS: Thank you, Michael. We really appreciate you sharing your experience.

(Applause.)

DR. EGGERS: And so with that, I think we really should break for lunch. When we come back, we have a couple questions about treatment approaches, and I think we've talked about meaningful benefits. So we're going to focus in on treatment approaches for a few minutes when we get back from lunch. We will

come back.

UNIDENTIFIED FEMALE SPEAKER: People were stopped coming into the FDA --

DR. EGGERS: Oh. We're -- we'll come back at 1:30.

Thank you very much.

(Off the record.)

DR. EGGERS: All right. Let's make our ways to the table. We have a lot to talk about this afternoon. Okay. All right. And as you are making your way to your table -- I want to make sure that we get as much in the discussion, so I'm going to get us started.

You can finish eating your lunches and use the restroom whenever you need to. What a discussion this morning. We want to continue the discussion. We're going to make one small change, and that is we're going to keep going with the patient input for -- I've been given the okay for another 20 minutes.

We're going to cut into some -- cut into a little bit of the afternoon session. So before we do that, let me just say what the afternoon is. The

afternoon is going to be about -- and what we're going to talk about with the patients will be useful, too.

We're focusing on, in the afternoon, drug development and looking for important, common issues to drug development for EPP that can help researchers, drug development, patient communities, and FDA as the regulator, understand how best to advise, support, conduct, and evaluate drug development efforts and programs.

So as I make my way around, I'll do the -- we'll do the town hall style again for the next 20 minutes. But I would like us to answer this polling question to kick us off. We want to understand your treatment approaches.

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. EGGERS: Oh yes, does anyone need a clicker? And you know what, the experts, you're going to need clickers, too, so -- for some part in here.

Okay. So as we get clickers there, you can go ahead. If you've got a clicker, you can check all that apply about what you are currently doing to treat

your condition or its symptoms. I'm going to make my way over here.

(Crosstalk.)

DR. EGGERS: The count? Okay. Now it should work, yes -- and if you -- only the patient or the caregiver who's speaking on behalf of a patient.

And welcome back to those of you on the web. You also can contribute through a polling question and keep web comments coming through to us.

We'll give it a few more minutes to let everyone get settled.

Okay. Yeah, I think we're ready for the polling results.

Graham, can you -- sorry I'm asking you to multitask. Okay. Cut off on the screen a little bit. We'll get to the other therapies not mentioned. We can't see I.

But as we discussed this morning, almost all of you are using protective clothing or masks. Can I have a show of hands? How many of those are you using an SPF type with some sort of protection built into it? Okay. So most of you then are using some sort of

protective clothing with an SPF. Okay.

And the lifestyle changes -- and I think we talked a lot about that this morning, the avoidance of the sun. And I think you have conveyed that very vividly this morning, so we won't get into that as much.

What we do want to talk about is your experience with pharmaceutical treatments. Can I have a show of hands? We don't have up here alfamelanotide. How many of you have taken alfamelanotide? Okay.

How many as part of a clinical trial? Okay.

How many are traveling to Europe? I know we have a few, okay, traveling to Europe for that. Okay. We're going to get to that in a minute, but let's go through some of these others first.

We heard one experience with cimetidine, and it was discussed this morning. So is there anyone who -- let's see. Not very many of you have had cimetidine.

Anyone had an experience with it you care to comment? Okay. We'll --

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. EGGERS: No, no. Well, wait for the mic so that the people on the web can hear us.

UNIDENTIFIED MALE SPEAKER 6: Hi. Yeah, I read, and I don't even remember where -- when about cimetidine possibly working, which the only thing I didn't like was the side effects of the Tagamet at the time. But I tried it for about six weeks and saw no -- nothing. It didn't do anything with it.

DR. EGGERS: Okay. Thank you.

UNIDENTIFIED FEMALE SPEAKER 12: I've been taking it. I had my doctor draw, like, you know, protoporphyrin levels just to see if I could compare. I have not redrawn them, but I've been taking it for a couple months. And I haven't really noticed, not significantly, any difference.

DR. EGGERS: Okay. All right. We have one more comment. Sure. Yes.

UNIDENTIFIED FEMALE SPEAKER 13: Hi. My daughter took it for one year. It was the over-the-counter dose times four, so she took four pills a day

for a full year. It did not have any effect whatsoever. And in fact, her protoporphyrin levels increased in that time.

DR. EGGERS: Okay.

UNIDENTIFIED FEMALE SPEAKER 13: So it went from 1,300 to over 1,600 -- so no effect.

DR. EGGERS: Okay. So let me just make the point right now that when we have discussions on treatments, it's not -- we're not making any statements collectively about overall experiences. It's not -- this is not necessarily a forum to focus on the -- to extol a benefit so much and the downsides or the ineffectiveness of treatments.

What we're trying to do as much is to hear about what would be meaningful -- if you saw improvements, what would be meaningful improvements. So I think we've heard from the three people who mentioned today that you didn't see improvements that you would have at all considered meaningful.

Okay. And how long -- you gave it six weeks back there. And you gave it a year back there. Okay. So you're giving it quite a long time to see some

effects. Okay.

Any of the other treatments?

Well, let's go into alfamelanotide. We heard a couple experiences up here. Is there anyone who would like to build on that experience we heard from the panel members this morning?

We'll go back there. Then we'll come up here.

UNIDENTIFIED MALE SPEAKER 7: Hi. I was actually in two of the trials, and I was able to have an active drug in the second time I participated. And I noticed an opportunity immediately to be able to do more. I go to Africa every year, and I worry about the experiences that I'll have, having reactions and so forth.

So I always wear my mask. On that particular year, I wasn't scared. And so I took chances and didn't wear the mask while I was there. And thankfully, I had no reactions whatsoever. And so I'm very thankful for that.

DR. EGGERS: Okay. Thank you.

Up here in the front.

(Applause.)

DR. EGGERS: We have one back here. Oh, okay. Okay. We'll go back there, and then we'll come up here. Okay. We want to make sure -- if we focus a little bit on people who have not talked as much, my apologies. Go back there.

UNIDENTIFIED FEMALE SPEAKER 14: Hi. I have two adult children with porphyria -- EPP. Six people total in our family actually have EPP. And I wanted to say thank you for this forum because being here today, just knowing that the FDA is listening, is just a wonderful feeling to have.

And I do want to say that some of the questions that were asked earlier really concerned me. And I mean this in the most respectful possible way that I want the FDA to understand that you're really talking about pain management and effectively treating pain management without narcotics is what everyone here seems to really be asking for and not just a little here or a little there.

But I think across the board they would like to have no pain at all. I'm sure that some of the

questions earlier -- you know, a mild -- would you rather have a mild reaction with this or a severe reaction with the other -- they don't want a reaction. And I think that --

(Applause.)

UNIDENTIFIED FEMALE SPEAKER 14: And I think that they're looking for pain management without narcotics. And pain management is widely accepted in the medical community. And it's something that they want for themselves here, and so do their families. Some people have even attested to having children that said it was so severe they wanted to kill themselves. It's a real thing.

It's -- you know, we have a 1 to tale -- 1-to-10 pain scale in a hospital setting. This is off the charts, you know. I don't have EPP myself, but I do have two children that went through it and are still going through this. And it's an off-the-chart pain.

And I think that, for me, that's just something I would really, really like you to understand, is it's not quantifiable or quantitative,

but that's pain. It isn't either one of those things, really.

DR. EGGERS: I think Dr. Kendall would like to ask a follow-up question.

DR. MARCUS: No, I just want to respond to that because I hope you don't misunderstand my intention. And I just want to give you my perspective again from my own experience in a different field, which I had just mentioned briefly at the beginning of the day, and that is treatment of HIV. That started out as an inevitably fatal disease and is a now fairly straightforwardly managed chronic disease. You know, the evolution of available therapies for that happened in small, incremental steps until there was a big breakthrough.

So that you know, AZT was the first drug that was approved, and it prolonged life by two months. Now, two months sounds trivial to me, but I don't think it was trivial for people who had AIDS. And that was a success, and that success was built on.

And so my purpose here is to understand how any product under development can have an incremental

impact on EPP with the goal of building on that success. If you define a path forward, stakeholders will step forward to go down that path.

And so I'm trying to understand the impacts on everybody here and how to really break it down into pieces that we can measure. And that's my intent. I don't -- I'm not sure what you've heard in my questions, and I've asked -- mainly been the person asking the questions.

And so I do have a concern that I've given you an impression that I would be satisfied with some small, incremental benefit. I don't -- I would never put a limit on what's possible, but I know that success often occurs in small, incremental steps.

DR. EGGERS: Thank you.

So any final comments on alfamelanotide? Okay.

ROB: Yeah, I'm Rob. I had the beta-carotene. I was on those trials back when I was a kid -- turned me orange, did nothing for me. I was on the trials for the alfamelanotide/Scenesse.

DR. EGGERS: You can say -- Scenesse is

easier to say.

ROB: I was able to work outdoors, didn't have to wear gloves, didn't have to have a hat, didn't have to have anything. I never once had an EPP reaction, not once -- no swelling, no nothing.

I actually experienced my first sunburn on the back of my neck. I rolled a bottle of cold water on it. It was gone. I don't know why people complain about sunburns. They really don't hurt.

(Laughter.)

(Applause.)

DR. EGGERS: All right. We'll have one --

ROB: And it was the best sunburn of my life. The following summer was my worst summer of my life when my 15-year-old granddaughter come to visit for the summer, and the first thing she said to me at the door was, "Papa, we don't get to go do those things we did last year, do we?"

(Applause.)

DR. EGGERS: Okay. One final comment.

MR. TURELL: All right. I'll be brief. I know I had the chance to speak before. But I

participated in the Phase II studies, and then I've been really fortunate for about the last year and a half to be traveling to Europe to recontinue treatment.

And I just have to say the -- speaking about what I'm looking for in a treatment, what Scenesse has done for me beyond my wildest dreams is just increased the amount of time I can spend outside before experiencing a reaction, that I'm trying to relearn, 20, 25 years of learned behavior of hiding from the sun.

And it's taken me now a year and a half to really even begin to understand my new limits, that every time I get the treatment and I get to spend time outside, I continue to try to push. And every time I do push myself, I'm amazed at how much more time I can spend outside, which I guess is really what I'm looking for in a treatment, that if a reaction is inevitable, if there's no way to really cure the disease, what I'm looking for is a way to just prolong the amount of time before I experience any reaction.

And FML -- Scenesse, just going to keep it

easy, has really just so surpassed my wildest expectations.

(Applause.)

DR. EGGERS: We do one more.

MS. BONSAGERN: Hi. I'm Gail Bonsagern, and my son, J.T., is a 22-year-old EPP patient. And his story is just like everybody else's here. He started symptoms at 2, took us 9 years for a diagnosis, and he suffered for 21 excruciating years with pain, both mentally and physically.

My son has been also very fortunate to be treated with Scenesse for the last year. We have made five trips to Switzerland. And you know, it is a major hassle and, you know, a major expense. But my prayer is that everyone with EPP has access to Scenesse. It has been life changing for my son, and I can't imagine going back to being without it.

DR. EGGERS: Thank you. We have a follow-up question.

MS. LINDSTROM: For the two gentlemen who just spoke, I'd like to understand a little bit further. When you articulated that you push yourself

and you're amazed at how the limits have extended, help me to understand how you are pushing yourself.

Do you push until you feel the symptoms, the stinging and burning? Or do you push? Do you increase time? What measure -- how -- define that a little bit more for me so that I can understand what you're saying.

MR. TURELL: Of course. Thanks for following up.

I think there are two different ways that I look at it. One would be the type of day that I'm willing to go outside, that I think as most people in this room would say that when you wake up and you see the bright, sunny day, you just don't go outside.

I've started to venture forth in smaller doses on days that I never would have gone outside previously, so in more direct sunlight on days when I generally would have stayed indoors.

The other one is as you said. I mean, I'm pushing until I begin to feel symptoms or until the fear and anxiety that we have discussed takes hold, that so for most of my life I've had maybe 20 minutes

before I would start to experience some sort of reaction.

Now I start looking at my watch, and I see 40 minutes, 60 minutes go past. And you need to fight yourself to really get over the learned behavior of, no, I've been outside way too long. And so I'm really trying to push that.

I'm still overcoming. Myself, really, is the biggest obstacle right now way more than the disease itself, just to relearn the behavior that I have learned over the last 25 years and really see how much farther I can take it.

And I've been on Scenesse now for the last year and a half. In that time, I've only one incident that I would really call a reaction, and it was so mild. It went away within about a day and didn't interrupt any of my normal activities. It was a slight tingling on my hands. That was after several hours outside.

So I'm looking now. I mean, it's getting tougher as it becomes the fall, thankfully, for all of us. But I'm trying to explore now the next month or

so, see how far I can push myself with these days. And I'm hopeful to get up into several hours outside.

DR. EGGERS: Did that resonate, both the two prong --

MS. LINDSTROM: Thank you.

DR. EGGERS: -- when you can go out and how long you go out? Okay. There are a lot of -- we want a lot of discussion.

I think -- do you have another follow-up question? Okay. Okay. Okay. We'll --

MS. IJAMES: I've been waiting a long time.

DR. EGGERS: Okay. We will take one more, please.

MS. IJAMES: -- follow up with Andrew. I was -- I'm in Phase I, also. But I am a very intense, I guess, patient. But I have always had the intensity of the lights. The wavelengths are really bad. The reflections are really bad for me.

So when I did the Phase I, for me, I was lucky. I did have the drug, so it was really -- I was very cautious. I didn't want to actually do what I had to do, but I did. And I was able to do it,

actually, on the beach down in Texas.

I went out there, and I'm going to do this. I was doing this. I'm 46, so I figured my life's half over. But I think about these children that are not over. And I think about what I went through, and I think about they need a chance. So I'm going to do what it takes for them to not suffer.

So I did this. And you know, I was terrified. But I remember counting the steps from Hotel Galvez to the beach and making sure that there was a runway and telling my husband here's my purse. Here's my shoes, just in case, you know, we got to run.

But from 10 minutes to 15 minutes to 20 minutes and, you know, by an hour I'm thinking we are really pushing this. But it is more of a we are definitely scared ourselves. But I think that it's just us after all these years being just taught to shadow jump. And the fear of going out into light is just -- we are living in darkness all of our life. But that's how we had to survive.

These children don't have to survive like

that. And I don't want them to survive like that. This drug actually is really amazing. I didn't have to survive like that on the beach. You know, it was -- we were testing it. I think I stayed out there for two hours, and I was still good.

So but that was it. I'm sorry. But I was done. I was like, okay, I'm really scared now. So we left. But I'm sure it probably would have been fine.

But that's all. I just wanted to just let you know that I believe that it's us. It's us that was probably the problem, but I believe that drug is amazing. I think it's going to help the children, especially and us to maybe finish our life out, maybe normal, whatever normal is for us.

DR. EGGERS: And what was your name again?

MS. IJAMES: Diana Ijames.

DR. EGGERS: Diana, thank you.

(Applause.)

DR. EGGERS: So --

DR. MARCUS: Diana, don't sit down. I have a quick question for you. Prior to spending the two hours on the beach, what would you say your limit

would have been? I take it you wouldn't step on the beach before trying it?

MS. IJAMES: Never.

DR. MARCUS: Okay.

MS. IJAMES: I am a five minutes max.

DR. MARCUS: Five minutes max?

MS. IJAMES: I was three years old -- three, four years old when my mother pretty much thought I was crazy and put me in the cellar. That's -- I mean, in the '70s, that's pretty much what happened. We thought -- they thought I was crazy. So I would scream and rip out my arms, and there would be bleeding. So I was punished a lot through my childhood.

So after many times of being tested for mental, I'm not. Yay.

(Laughter.)

MS. IJAMES: And then the allergy tests, all the needles -- no allergies. Yay. But I think SLU, St. Louis University, was able to find -- by the time I was seven -- that there was something, but there was no cure. But five minutes is max. So unfortunately,

it's just a real intensity.

DR. MARCUS: And just one more question. So you described just trying once to go out on the beach for two hours, and then you sort of retreated to your usual lifestyle. Did you -- were you able -- did you have any comfort level in terms of -- you know, and I found it very helpful to talk to Madelyn and her parents about what, you know, light therapy gets her, which is walking from the parking lot into a store.

And so maybe a better way to quantify benefits is through activities. And I -- it sounds like the beach was kind of an extreme range for you. But were you able to do other things that was --

MS. IJAMES: I was able to take my son --

DR. MARCUS: -- less --

MS. IJAMES: -- places. He was actually 10 at the time. And having a little boy wanting to go outside all the time, it was nice, you know, because I only have one child. And I only get one child, so I was able to take him, not dad. So it was an amazing time for me.

DR. MARCUS: So you were able to take him

outside?

MS. IJAMES: Play ball.

DR. MARCUS: And you played ball. Okay.

MS. IJAMES: We went fishing. Yay. And we got to go camping. That was exciting -- not really. But there was all kinds of things that I got to do with my son that I would never have been able and I still can't do it right now until it's nighttime.

Also, the seasons, like if I do go camping, it has to be before May because the heat really bothers me, the intensity of the heat, the waves coming off of cars or lights or anything, just the bouncing of reflections.

My home is completely tinted. You can see out. You can't see in, but the reflections bounce back off. All my cars are tinted. I have three of them, but they're all just really darkened. And it's just my lifestyle.

My whole entire company -- I have a factory. All the lights have been changed out. They're all LEDs because the fluorescents, they burn me completely. And it's just -- my lifestyle is just

completely awful, and it's just -- it does.

It's just an intensity of pain for me that I have to do this, and I have a handicapped parking. I have to park right there by the door, and I run. I just run, and that's my life.

It's five minutes. I've got five minutes. So -- but after that, yes, I was able to, I mean, actually go shopping. So I was able to go to St. Louis. And there's -- I got to be a person for once, not just a runner. So …

DR. EGGERS: Thank you very much, Diana.

(Applause.)

DR. EGGERS: We're going to have to wrap up this portion to make sure we get into the scientific. One, we're interested in just a show of hands about phototherapy. Not very many of you mentioned currently doing it.

How many of you have done it at some point? So okay. All right. And hands up if you found that effective for you. Hands up if it didn't have a meaningful effectiveness for you. Okay. Okay.

All right. Then, first of all, let me --

this would have normally come before lunch, but on behalf of my FDA colleagues and my teammates, thank you very much for this discussion and for, I think, the respect that we have for one another to let each other speak and to really build on. I thought it was excellent, building upon what each other was saying and resonating. You have a community here, and that came out strikingly strong.

So a round of applause, please, for you. Give yourselves a round of applause.

(Applause.)

DR. EGGERS: Yeah, it was -- and now we're going to move into a more technical discussion, a more scientific discussion, about critical issues that are currently at the forefront in trial -- drug development for EPP.

Before we do that, I'd like to go through and introduce -- have the expert panel members introduce themselves.

And is Dr. Teng -- Joyce, are you in -- are you here? Maybe she had to step out.

Yeah. Come on up. Okay. So if we can just

go through where you are and where you're from.

DR. BALWANI: Hi. My name is Manisha Balwani. I'm the co-director of the Porphyria Center at the Mount Sinai School of Medicine. And EPP is my clinical and research focus, and I've been involved in taking care of EPP patients for about nine years now. And I've also been an investigator on the alfamelanotide trials.

DR. DESNICK: I'm Bob Desnick. I'm a medical -- I'm board-certified in medical, clinical, biochemical and molecular genetics. I trained in pediatrics, did a pediatric residency. I'm at Mount Sinai where I'm the past chair of the Department of Genetics and Genomic Sciences.

We run the Porphyria Center. We do most of the diagnosis for porphyria in America, all the different porphyrias. I am the PI of the NIH-sponsored Rare Diseases Clinic Research Network on porphyria where we've evaluated patients in six centers.

And there's a couple of us -- Carl Anderson (ph) and John Philips (ph) and Manisha -- who are here

representing the Porphyria Consortium. I was also the PI of the Phase II and Phase III quinuvel (ph) trial. We've had a lot of experience with EPP. In the Porphyria Consortium, there are now about 230 patients who have been seen, examined, and biochemically and molecularly confirmed.

DR. EGGERS: Thanks.

DR. MINDER: My name is Elisabeth Minder. I hope you understand my English.

I'm a trained -- I'm trained in internal medicine, clinical pharmacology, and laboratory medicine. I'm the head of the Reference Center for Porphyria in Switzerland. We have more than 500 patients in Switzerland.

We were starting with alfamelanotide Phase II trial in 2006, and then I was principal investigator also of a Phase III trial. Since 2008, we have access on a special access team for alfamelanotide for Swiss patients until now. And we have a long experience with development of trials, and we have a decade of experience how to measure efficacy in EPP.

DR. EGGERS: Thank you.

DR. LIM: I'm Henry Lim. I spoke to you all before. I'm from Detroit, Michigan. I'm a dermatologist by training. I'm Chair of Dermatology Department at Henry Ford Hospital. I've been involved with porphyria since -- I mentioned before -- since I was a resident.

And now I cover all aspects of photo-dermatology, which is a subarea in dermatology, to look at the beneficial as well as the side effects of sunlight, including photo protection, including of course the porphyrias. And I was sent as also a participant in the trial of the alfamelanotide that was published.

DR. EGGERS: Thank you.

DR. TENG: Joyce Teng. I'm a double board-certified in dermatology and pediatric dermatology. My special interest is genetic skin diseases and drug repurposing, and I have no other financial disclosures. I did not participate in this particular clinical trial.

DR. EGGERS: Great. Thank you.

We're now going to have two presentations to level-set on the drug development and FDA's regulatory process.

So I'll ask Paul to come up.

UNINDENTIFIED FEMALE SPEAKER 15: Is Dr. Poh supposed --

DR. EGGERS: Excuse me?

UNINDENTIFIED FEMALE SPEAKER 15: She's on the panel. She just wasn't --

(Crosstalk.)

DR. EGGERS: Is she here?

UNINDENTIFIED MALE SPEAKER 8: She is here.

UNIDENTIFIED FEMALE SPEAKER 15: -- on a panel but confused about --

DR. EGGERS: Is she here? Is she here to -- okay.

Then come on up. Yep.

And Dr. Poh, if you could introduce yourself, please.

DR. POH-FITZPATRICK: Good afternoon. I'm Maureen Poh-Fitzpatrick, and I'm at Columbia University in New York City. And I have been a

researcher on protoporphyria since the 1970s. I was principal investigator of a NIH-funded research laboratory, and we looked at basic and clinical research in EPP.

I've seen many patients over my career, and I think I have some insight into what may be going on, so I'm very happy to participate in any way I can today.

MR. PHILLIPS: Great. Thank you.

So as mentioned, my name is Paul Phillips. I'm a project manager in the Division of Dermatology and Dental Products here at the FDA. And this afternoon, I'm going to give you a very brief overview of the drug development and regulatory process and the different roles that are played within that.

During my overview, I will discuss the stages of development, beginning with discovery and moving all the way through the post-approval stage. Listed here, you'll see a few definitions that will come up today. And I will use a few of these acronyms as well as the definitions themselves. Hopefully, it will help you understand what I'm referring to as I

use them.

A point I'd like to reiterate that was mentioned earlier by Dr. Marcus and when she touched on it in her opening comments was that the drug development process is really initiated and carried out by companies, physicians, and other entities that are independent of the FDA. The FDA's role really is just to simply regulate the process to ensure the protection of the public health. So …

The drug development process begins with discovery. This particular step is not one that the FDA regulates, but the next step, the non-clinical step, which is carried out in the laboratories, is where FDA begins their regulation.

We provide good laboratory practice guidelines for sponsors to follow. And the purpose of this step really is for sponsors to gather information sufficient to support the submission of an investigational new drug application, which as you noticed on the previous slide, allows an investigational product to be given to humans.

One of the purposes -- excuse me. So with

that, let's take a closer look at what specific information is required in order to submit an IND that the FDA could then allow an investigational product to be given to humans.

Listed here, the first two bullet points you'll see are both what we call product quality as well as pharmacology and toxicology information that sponsors will gather in order to support the safety of a product and be given to humans.

If a product has already been given to humans in either another country or in previous trials, then we also like to see the experience that was previously seen in humans with that product to help us make our decisions.

So once the FDA receives a new IND, the sponsor must wait 30 days before they can initiate studies of the proposed clinical trial. During this time, the FDA reviews the information in the IND to determine if the study in humans is safe to proceed.

At the end of those 30 days, if we haven't discovered any potential safety concerns that we think would, you know, be of harm to the subjects, then the

study is allowed to proceed at the end of those 30 days.

First in -- human studies typically begin in Phase I of clinical development. I'll talk a little bit more about what that means. So Phase I of clinical development is, again, first in human studies generally. It's typically done in healthy volunteers, although there are exceptions. We heard one of those here a few minutes ago.

The starting dose of the drug is low compared to the dose that would be expected to produce efficacy or adverse events. And the purpose of this phase really is just to assess the safety in humans, to gather PK data and other information, such as the effect that food may have when using the drug. These studies, as well as all clinical trials, should be conducted according to good clinical practice guidelines, which are endorsed by the FDA.

After completion of Phase I studies, the next stage is Phase II of clinical development. New INDs for drugs which have been previously given to humans will often start in this phase. During this

phase, there's also a continued opportunity for sponsors to interact and receive feedback from the FDA on their development program.

Specifically in Phase II, these studies are typically done in volunteers with the disease of interest as opposed to health volunteers that we talked about in Phase I. These studies are usually dose ranging to determine the optimal dose for treatment.

Sponsors look for trends of evidence or efficacy of the drug against the disease. Sponsors also continue to assess the safety in humans, gather PK data and other information, such as the food effects that we mentioned previously.

One of the opportunities during this phase that sponsors have to interact with the FDA occurs at the end of this phase when sponsors can come and meet with us with what's called an End-of-Phase II Meeting where the Phase II study results and the sponsor's plan for confirmatory Phase III clinical trials can be discussed. And the FDA provides feedback on the sponsor's proposed plans in order that those studies

can be designed in a way to gather the appropriate safety and efficacy data that will eventually be needed for marketing application.

The next and typically last phase of clinical development is what we call Phase III. Again in this stage, there's additional opportunities for interaction and feedback with the FDA. Phase III trials are conducted in volunteers again with the disease of interest.

Now what's important is that the drug that's given has to be what we call the to-be-marketed formulation, and the dose that the drug will -- basically, the product has to look like what it's going to look like when it's in -- with what the company intends for it to look like when it's going to be marketed.

The purpose of this stage is to generate what we call substantial evidence that the drug product is effective for the intended use. This standard of substantial evidence is set by the Food, Drug, and Cosmetic Act and is defined in the Code of Federal Regulations as being generated from "adequate

and well-controlled trials."

So generally, to the FDA this -- we interpret this to mean that we generally recommend that sponsors conduct two adequate and well-controlled trials in order to confirm the product is effective for the intended use. These trials also add to the growing safety database that we've been gathering over this period of time.

Again, in this stage, another opportunity for feedback with FDA occurs at the end when sponsors have the option to meet with the FDA to discuss the content and format of their eventual marketing application so that when it comes in, it's complete and in a condition that we can review it.

So once an applicant has then generated all of this data and gathered everything that is needed, they can submit what's called a new drug application or a biologics license application -- that's the specific term I've been referring to as marketing application -- for review by the FDA.

One point to note -- the FDA does not solicit these. These are submitted at the choice of

applicants whenever they feel that they have sufficient information to submit one of these applications. So they may do that at any time.

The FDA review of a marketing application actually has quite a few steps. And generally, it lasts anywhere from 6 to 12 months, depending upon the type of application that is submitted.

The marketing application review process -- I'm going to go into a little bit more detail because I think this is one that's important. The first step that FDA takes after we review an NDA or a BLA is to determine whether or not the application is complete.

In other words, does it contain all the data elements that are outlined by the Code of Federal Regulations? Applications for a drug that contain an active ingredient never marketed before in the U.S. typically allow an extra two months for FDA to make that determination of completeness.

If an application is complete, it's filed, and the scientific review then begins. During the review of the products -- of products with a new, active ingredient, FDA will often hold a public

advisory committee meeting to gather outside expert input.

There are discussions about the product labeling that occur between the FDA and the applicant during the review process. Substantial evidence is determined by FDA's scientific review of the data submitted in the application. This determination, along with other recommendations from the review team, contribute to an overall benefit risk decision, which was mentioned earlier, again, by Dr. Marcus.

And that means just the decision about whether the benefits of the drug to the intended patient population are likely to outweigh the known or potential risks of the drug to the intended population.

Based on that benefit risk assessment, a final decision is made by the FDA to either approve the drug product for marketing in the United States or to issue a complete response, which is a non-approval that contains deficiencies for the applicant to resolve before the drug can be approved.

For drug products which are approved, the

development of the product then continues in what we call the post-approval or post-marketing stage. In the post-approval stage, FDA continues to monitor the safety information of the drug product from a variety of sources, including adverse event reports, which we receive in our new FDA Sentinel system, which has recently been stood up.

Sponsors continue to develop their product in a variety of ways. I'll mention two. One is an example of them addressing the Pediatric Research and Equity Act, or PREA, to study the drug in children to generate information for labeling that will guide prescribers who treat children with the disease of interest.

These required pediatric studies are often not done, although there are exceptions to this. But these are generally not done until after sufficient safety information is gathered in adults. Therefore, because of that, a drug is often first approved in adults, and then the pediatric development occurs post-approval in children.

Another example of the development and post-

approval stage is when a sponsor chooses to investigate the use of their product to treat other diseases than that which it was initially approved for. In that case, sponsors usually start back again at Phase II of development and work their way iteratively through the process we just described until they have sufficient safety and efficacy data to submit to the FDA for review of a new indication.

This iterative process of additionally gathering safety and efficacy data throughout the lifecycle of a drug, in particular in the post-approval stages, continues until a company comes to a point where, for a variety of reasons, whether for safety or business decisions or other reasons, they may choose to stop marketing the product and manufacturing their product.

And that typically marks the end of the drug life cycle in the development process as we think of it as a whole.

So with that, that concludes my remarks, and we'll turn the time now to Dr. Kathryn O'Connell.

DR. O'CONNELL: Good afternoon. My name is

Kathryn O'Connell, and I'm a medical officer in the Rare Diseases Program, which is a program within the Center for Drug Evaluation and Research.

And before I say a few words, I would like to thank you all very much for coming here today and helping us learn about this disease. It's very important to us, and we appreciate it.

We're a little short on time today, so basically I'm just going to build on what Paul has already talked about by talking a little bit about the approval process in the context of rare diseases. And Jonathan and I are both on the panel this afternoon. So if there's anything that's of particular about this topic or other rare disease topics, we can maybe work on it then.

So the first thing that I wanted to -- like we said this morning, get everybody on the same page -- is what are we talking about when we talk about a rare or an orphan disease? So a rare disease is defined in the Orphan Drug Act -- and many of you probably already know this -- as a disease or condition that affects less than 200,000 people in the

United States. That's generally what it means.

And so an orphan drug is a drug or a biological product that's used for the prevention, diagnosis or treatment of a rare disease in the United States. So with that in mind, we can look at actually what the Orphan Drug Act did.

So that was in 1983, and the Orphan Drug Act actually was enacted specifically to stimulate product development for rare disease conditions, as we just defined it, for the diagnosis, prevention or treatment among other things. There are other things the Orphan Drug Act does.

But among the major things that it does are financial incentives that were -- that are designed to encourage sponsors to study -- you know, to study and develop drugs.

So this is the reason I brought those points up because this is a really important point. The Orphan Drug Act did not alter the statutory standard for drug approval. And so what that means is that regulatory requirements and the process for obtaining marketing approval in the United States are the same

for drugs granted orphan designation through the Orphan Drug Act as for common disease drugs.

And this surprises people. And sometimes I've even heard people say, oh, that must have been an oversight, you know, when they made the Orphan Drug Act, but it isn't. It was not an oversight -- I'm going to talk about why -- because the real principle here is that people affected by rare diseases deserve the same level of drug quality, safety, and efficacy.

So you're asking yourself, like most people do, well, how can the same standards apply to a disease where there may be only 35 people compared to diseases where there's millions of people.

And the fact is that special standards for orphan drugs are unnecessary because the regulations that FDA works under already had in place specific language about flexibility and judgment on the part of the FDA in applying those standards.

And it doesn't specifically call out rare diseases. But it calls out the special circumstances and conditions of diseases, and then flexibility is applied as needed. And so, you know, in fact, many

rare diseases that are approved, flexibility was and is applied during the decision-making process.

So what are the approval essentials? So in the United States, what is the bottom line? What do you need? So the first thing is you need substantial evidence of effectiveness for treatment of the proposed indications. So the indication is, you know, the disease.

The second thing you need is a demonstration that the benefits of the drug outweigh the risk for the patient population for which the drug is indicated. And then the third thing is that there has to be a manufacturing process in place that ensures what the drug is in the marketplace and the strength of it, the quality, et cetera.

And then the fourth thing is that there needs to be, you know, evidence-based drug labeling. So labeling isn't the thing on the bottle, but it's the prescription, the sheet of information that the doctors get, that you get, that adequately guides prescribers and patients so that the drug can be used safely and effectively, essentially describes what is

known about the drug.

So again, this is such an important point. I just want to mention a couple things about it. So the regulatory requirement for approval in the United States, as Paul mentioned already, is demonstration of substantial evidence of effectiveness. And that generally requires studies designed well enough to distinguish the effect of a drug from other influences, such as a spontaneous change that would have happened even if, you know, the patient hadn't been exposed to the drug.

And examples of spontaneous change would be a placebo effect or a biased observation. And biased in this case doesn't have the context that it does in the outside world. It just means that it's an observation that isn't -- it -- where there could be things that affected the observation that weren't planned.

So basically, that's the requirement. And then as I already said, the benefits need to exceed the risks under the conditions stated in the labeling. And as Paul mentioned, the usual approval standard is

two adequate and well-controlled studies.

However, as I noted before, FDA has applied the flexibility that I talked about, very often to rare disease drug review and approval. And in fact, in 1997, the FDA Modernization Act, you know, specifically stated and clarified that FDA can consider data from one adequate and well-controlled clinical investigation with confirmatory evidence to constitute substantial evidence.

If you want to know more about this, this is the name of the guidance that you can refer to. You can get it on -- you know, on the Internet. And it talks about the scientific reasons why FDA doesn't generally rely on a single study.

And it's usually reserved for situations where there's a clinically meaningful effect on mortality, irreversible morbidity or prevention of a serious disease and situations where it really is not feasible to do a confirmatory trial. So basically, it's a judgment call, as we talked about a few minutes ago.

And the last thing I'm going to just say

here -- and then I'm going to stop so that we can get sort of back on schedule here -- is the safety piece of this. So the safety evidence for approval to support, you know, a marketing approval, is also a judgment call.

And it's based on the overall assessment of the risk and the benefit within the context of the disease. So again, you need, you know, a demonstration of substantial evidence of effectiveness so that you got that part of the equation. And then the benefits of that drug must exceed the risk under the conditions stated in the labeling.

So I think I'll stop there. And like I said, we're on the panel. And during the panel discussion, if you want to bring any of this up, please do.

Thank you.

(Applause.)

DR. MINDER: Ms. Marcus, dear friends and colleagues, I thank you very much for me to present challenges in clinical trial design in EPP.

Here you can see my conflict of interest

statement. Actually, I never had a personal benefit from cooperation with pharma companies. My motivation is the wellbeing of my patients.

Our exercise in porphyria covers more than 45 years. We care for 500 Swiss and many patients -- many porphyria patients from other countries. Since 1990, our focus is on EPP, and we have cared for more than 100 patients.

Our analysis of beta-carotene trials illustrates the necessity of high-quality trials. Low-quality trials result in falsely high efficacy. The recently published cimetidine trial would nicely fit in this diagram and would localize here.

So first challenge in trial design is to define EPP. It is simple for porphyria experts -- phototoxic episodes since infancy or early childhood and significantly increase protoporphyrin. Symptoms and burns (ph) in a designated period gets described for Phase III for the cimetidine trial is characteristic of congenital erythropoietic protoporphyria, which is a different disease.

The second challenge is to find the

rationale for treatment. Skin barriers to prevent photo activation of protoporphyrin, scavenging of oxygen radicals or other inflammatory compounds generated by light activated protoporphyrin, mitigation of local skin inflammation and improvement of survival and inhibition of ALA-synthase 2 are rationales used until now.

In the last decades, our team applied without success all compounds with stars on this slide. Thus, we gained a broad experience with ineffective treatments in EPP, including self-tanning, sunscreens, beta-carotene, cysteine, antihistamines.

With carefully dosed UVB treatment, we found a slight -- a really slight improvement in some patients. However, most of them did not tolerate it because it was too painful for them. The only drug that was highly effective was alfamelanotide.

We did not use cimetidine because its preclinical evidence is insufficient, as shown on the next slide. Every publication on cimetidine in any kind of porphyria refers to the 1984 publication of Marcus (ph). He showed in whole animals a short lift

decrease of ALA-synthase activity for 30 minutes followed by an increase to a level higher than initially.

Thus, second, cimetidine did not inhibit ALA-synthase activity directly. Thus, the observed decrease is due to a liver specific regulation of ALA-synthase. As in bone marrow, ALS-synthase activity is definitely regulated. An effect of cimetidine on protoporphyrin synthesis in EPP is unlikely, and I can add I just heard yesterday that John Philips and Bob Desnick have additional data on this.

So the challenge is similar for all rare diseases. Complexity of disease negatively affects outcomes. High variability of symptoms reduces statistical significance. Adaptation due to early onset in life leads to an overestimation of quality of life before an effective treatment.

Minor positive changes may be important to patients. Also, we as healthy persons may consider them as insufficient. We know these problems also from quality attested life years.

Last, if there is no preexisting effective

treatment, it is impossible to validate an outcome instrument.

But let's go back to EPP. EPP is not the simple sunlight sensitivity, and in EPP, irradiants does not correlate to the extent of photo damage.

We all agree that EPP patients are sensitive to light, to direct sunlight, to sunlight passing through windows and to sunlight reflections at the beach or in the snow. However, bright sunshine is less offending than overcast sky.

Many patients suffer from indirect light, both outdoors and indoors, and more and more patients complain about artificial lighting, especially the new energy saving bulbs. Wind, temperature and air humidity modifies symptoms.

We even do not exactly know which wavelengths are damaging. Blue, we all agree yes because it's a major absorbance found of protoporphyrin. Red, most likely because, in photodynamic therapy, it is a yet organic (ph) local EPP. It uses red light.

As we emphasized before, many patients react

to UV. Also, protoporphyrin does not absorb at these wavelengths. And we have determined that protoporphyrin has absorbance bands in the infrared. And at least during phototoxic episodes, patients are very sensitive to heat.

The effect of latitude is illustrative that the lack in correlation of irradiants and photodamage. Also, irradiants is highest in equatorial regions. EPP patients have reduced symptoms or even no symptoms in tropical areas.

As a young physician, I recommended the parents of my EPP children to spend their holidays in the northern countries because I thought EPP children may benefit from reduced light intensities. That was wrong. Symptoms are increased in higher latitudes.

Phototoxic damage does not follow certain rule that a certain intensity of an offending action determines a certain degree of damage. Well known in medical literature and also cited today is the priming phenomenon.

If a patient is light-exposed one day, he or she is more sensitive to light the next day, but it is

even more complicated. Patients speak of a light account for four, five or six days. They can expose to light, but when their light account is empty, they get really sensitive to light and easily burned.

So extraordinary disease variability is illustrated by the 14 times variation of its biomarker, protoporphyrin, in the Swiss cohort. The same is true for United Kingdom patients, if you just look at the X values of the lower graph.

This graph also makes a correlation between protoporphyrin concentration and quality of life, as measured by the dermatological quality of life index. The authors found a positive correlation. However, higher life quality with higher protoporphyrin levels is clinically nonsense and this qualifies the TLQUI for measurement of quality of life of therapeutic effects in EPP.

This leads us to the first challenge, the endpoints. Sunlight exposure and pain intensity are possible but complementary endpoints. Why complementary?

On therapy, one patient may tolerate a

certain pain level and expose longer to the light. Another one may not need to expose longer to the light but he happy if he has less pain. If only one or the other is measured, outcome measurement loses sensitivity.

The only biomarker I can think of in EPP is protoporphyrin. Its value is limited in a treatment intending to its reduction. That is cimetidine. Quality of life is an important outcome in EPP. TLQUI and SF36 do not qualify. EPP specific quality of life questionnaires has high discriminatory power.

As you see, the black or the untreated patient and the open scales are the treated patients by alfamelanotide. There's also a sensitive method as seasonal effects by a slight decrease during summer months is observed during alfamelanotide treatment, which is a clinically reasonable finding.

Let's go back to the complementary endpoints, sunlight exposure and pain intensity. The X-axis of this graph displays 15 minutes block, and the Y-axis pain intensity.

We asked the patients imagine you get a new

treatment against EPP symptoms, and at a sunny, summer day during lunchtime, you're outside in the sun for a certain time, which results in a certain pain intensity. Estimate the effectiveness of this new treatment.

You can see that the patient rated effectiveness to be 0 if they suffer from a pain intensity 10 after one quarter of an hour of sun exposure. That's meaningful. But look at that. Patients estimated the effectiveness to be 70 percent if they do not have pain after only 15 minutes sun exposure, and it goes up to 90 percent after half an hour of sun exposure without pain.

What I said before, minor effects, what we as healthy would question to be a substantial benefit are important to patients. Interestingly, Longendock (ph) and coworkers used exactly this outcome -- sun exposure without pain in the Phase III trial on alfamelanotide.

Their results on 89 U.S. and 74 European patients demonstrated a significant benefit of alfamelanotide. This endpoint is not the surrogate

marker. It's a direct measurement of the limitation caused by EPP, and the number of patients in a disease of the rarity of EPP is impressive. These trials as such will fill high-quality standards.

Certainly, pigmentation or skin coloring may induce a bias in a double-blind trial. Corbit (ph) found no effect of beta-carotene versus placebo. Also, he noted unblinding of spasi (ph) active compound. His outcome was measured by -- measurement were diaries. Such diaries are robust against unblinding. In contrast, Norris (ph) emphasized a rather strong placebo effect using retrospective questionnaires.

The last challenge is to convert statistical and clinical efficacy. Clinical efficacy, in my mind, is not a scientific term. It's common sense of healthy persons. Patient's attitude may be different. If no validated comparator exists, statistical significance should be considered as clinical efficacy, in my opinion, especially in a rare disease.

Averaging sun exposure per day results in misleading values as rainy days, staying inside due to

work, habit. And also, we have heard lifelong conditioning dilutes the effect. In EPP --

(Applause.)

DR. MINDER: In EPP, the contribution of patients to validate clinical efficacy is crucial.

They informed us on a recurrent -- recurrently on ineffective treatments, as we have heard before. With respect to alfamelanotide, patient considers this drug as lifechanging. They sacrifice a lot of personal money and time to get it, and they adhere to long-term treatment under routine conditions -- in our eyes, a compelling evidence of efficacy.

I thank you for your interest.

(Applause.)

DR. EGGERS: All right. Thank you for three very informative presentations.

We are now going to move into a facilitated discussion with the panel members. I think we'll have about an hour or slightly less. I will try to squeeze as much as we can out of this as well.

I'm going to stand here because, well, frankly, I need to lean on something.

(Laughter.)

DR. EGGERS: So I will be standing here.

The discussion topics, broadly speaking, will follow the themes that -- many themes that were outlined by Dr. Minder's presentation, other things identified by FDA as being important to talk about, considerations when defining the EPP trial population, choosing the appropriate endpoints that can be reliably measured and interpreted and that demonstrate a clinically meaningful benefit, what types of measures, other clinical trial design considerations, and then some on patient and caregiver experiences in clinical trials.

Now, this is more than we can cover in an hour, so I will ask my colleagues at FDA to guide where you think is important. And we also have a polling question to elicit from the experts in a few minutes what you think are important considerations for trial design as well.

But first we want to -- we have a couple polling questions for those of you in the audience, the patients and caregivers on behalf of a patient as

well as on the web. We're thinking about clinical trials now, so we're moving into thinking about your participation in a clinical trial.

And the first one is have you or your loved one ever participated in any type of clinical trial studying an experimental treatment for EPP? So A for yes and B for no.

Okay. So this is so deceiving. Don't look at the size of those bars. It is about 50/50. Half of you in here have participated in a clinical trial, so we have a wealth of experience here in the room.

And on the web?

MR. THOMPSON: About 40 percent for yes and about 60 percent for now.

DR. EGGERS: Okay. Thank you for participating in clinical trials. It is vital to the development of safe and effective drugs.

We'll move on. So if you or your loved one had the opportunity to participate in a clinical trial, in a future clinical trial, to study an experimental treatment, would you consider participating? A, if yes, it would depend on many

factors, but I'm generally willing to consider participating. B, no, I would probably not consider participating. Or C, maybe, I'm not sure if I would generally be willing to participate or not.

Okay. So three-quarters of you in the room today would generally -- that you are willing to consider participating with some of you saying no and about a fifth with maybe.

Okay. We're going to have one more polling question to get into some factors you might take into account. And I can already tell you we haven't gotten the right factors. There are many, many factors.

Can we go to the next slide?

By the way, we only get to go to I on here, so we only get nine things to put up on our polling. And these were the factors that we thought might be a place to start when thinking -- that you might be thinking about if you were deciding -- the biggest factors you would take into account if you had the opportunity to consider participating in a clinical trial for an experimental EPP treatment.

So we'd like you to think through these and

choose up to three factors that would weigh most into your decision-making if you were considering participation. A, the complexity of the study requirements, what you have to do on treatments --

UNINDENTIFIED FEMALE SPEAKER 12: Any trial?

DR. EGGERS: For a trial. For any trial for experimental EPP treatment. Okay.

UNINDENTIFIED FEMALE SPEAKER 12: Not trials we've already done. You want to us --

DR. EGGERS: No. A new trial has come. Imagine a new trial. You are thinking about whether you would like to participate. What are you taking into account? The complexity of the study requirements, the things you have to do.

B, the eligibility criteria, such as the exclusion requirements. C, the location of the study site. D, concerns about side effects. E, the possibility of a placebo as a control. F, the need to stop any current medications. G, the trial duration, so how long that trial is going. H, concerns about informed consent procedures. Or I, other.

And H would be informed consent procedures

for you or your child. Any of these would be the considerations for your child if that -- if your child is the one participating.

Okay. So a wide range of thoughts and perspectives out here with half of you saying the location of the study site. And then about four-tenths of you in here are saying concerns about side effects and the complexity of the study requirements.

Okay. So we will be coming back to you to -- maybe through show of hands or for a few comments as we continue going through the rest of the panel discussion.

But we thought it would be important to prime this discussion by thinking what is important, what might be on study participant's mind when you think about clinical trials.

Okay. So with that, I'm going to segue --

UNINDENTIFIED FEMALE SPEAKER 12: I'd like to hear what Dr. Phillips's evidence is.

DR. EGGERS: You know, there --

UNINDENTIFIED FEMALE SPEAKER 12: Is that possible?

DR. EGGERS: I'm not sure if we're going to be able to answer the question now. The question was about evidence that was raised during one of the presentations, if you're on the web and can't hear in the room, and whether that evidence can be shared.

I'm not sure if we have the answer or if that's within the scope of today's discussion. However, I would encourage that to be submitted to the public docket, nonetheless.

And Kendall, do you --

UNINDENTIFIED FEMALE SPEAKER 12: I mean, here's here. I thought maybe he could --

DR. MARCUS: So I just want to give a little bit of direction to everybody about the purpose of this. And I just want to build on the comments that I've already provided in that I think that successful treatment is often a series of small, incremental steps.

And our purpose today is fairly broad reaching. I want to acknowledge that many people in the room participated in the clinical trials of alfamelanotide. I don't want to dwell on that because

there is other work that can be done. And as I said, why would you ever stop at a certain amount of benefit, similar to the transformation of treatment for HIV?

So in that vein, I would like to think broadly about clinical trials so that we can build upon the experience that we have in order that a clearly -- that we can learn from the past to have clearly defined and improved ways of measuring benefit and success.

And then the last piece I just want to keep in mind for everybody is that, particularly with a rare disease, I think the most difficult clinical trial to design would be one for pediatric patients. And I would like to know, you know, what children -- what treatments can be offered to children and what can be made available to them.

And now we're talking about an extremely small population from which to draw in order to determine a safe and effective dose. And so we have to think very carefully. And this is why I am asking a lot of questions, just trying to parse out small

increments of benefit that can be measured successfully in a small number of patients.

So I hope that helps you understand the purpose of this discussion today. I don't want it to -- I just would like people to think broadly and think in a forward manner. I think -- I've heard from a number of patients today that they're here because they'd like to see the children in the room benefit from being here. And so do I.

And as I said, that's going to be a particular challenge, defining effective treatments for children because, obviously, you want any patient to be treated as soon as they're diagnosed.

So I hope that's helpful. I think I'm rambling now. So …

DR. EGGERS: There's also -- I'll just put a reminder. There is a time for open public comment at the end of the day. The signup sheet is over by Meghana, if you raise your hand. We have 15 minutes set aside for open public comment.

Meghana, can you --

MS. CHALASANI: Ten.

DR. EGGERS: Ten? I'm sorry. We have 10 minutes set aside for open public comment, and we can take up to six people.

So Meghana, can you stand so people can see where you are? Great.

Okay. And I've also been notified that the kiosk where you bought your snacks and lunch will be closing in five minutes. So if you need a last snack, please do so now. Okay.

With that said, as a way to guide discussion for the next 45 minutes or 50 minutes, we're going to ask the experts only a polling question.

Does everyone have a clicker? And it's right there in front of you. You can look on the screen there. Do all of you have a clicker? Okay.

Again, there are numerous challenges in designing clinical trial programs and trial designs. But of the following factors, which are the most significant do you think to address in designing a robust and feasibly clinical trial?

You can choose up to three factors -- understanding that natural history of EPPA;

appropriately defining the trial population; choosing endpoints that are meaningful to patients; D, choosing endpoints that can reliably be measured and interpreted; E, choosing an appropriate control; F, selecting an appropriate trial duration; G, addressing the complexity of study protocols and requirements for the participants; H, recruiting and retaining trial participants; or I, something else.

Okay. Oh, we have seven. Did all the experts answer? Just the experts, please. Okay. Okay.

So of -- this is -- again, this is not a scientific poll. It's just to see -- get a gauge on where you might be in your thinking about what's important.

And choosing endpoints that are meaningful to patients was by five of you, followed by choosing endpoints that can be reliably measured and interpreted. So we will get at that balance in a little bit.

Okay. So the considerations when -- do we want to -- we'll start with defining the EPP trial

population. And the question -- we'll just go -- we're going to go down the line. And when you think about defining a trial population, let's do a round robin. And briefly -- think is most important to consider when defining the trial population. And then we'll follow up that my colleagues might have something more to tie on for that.

But first, unless you have a clarifying question, we'll go through each of you. Very briefly, say what's the most important, if this is your area of expertise, about defining a trial population to keep in mind.

DR. DESNICK: Let me kick it off. I think the most important thing that you mentioned was understanding the natural history of EPP. You cannot design a trial unless you really understand that. You cannot pick the endpoints until you understand that, and everything else falls up from that.

And I thought Henry Lim did a very good job this morning when he quoted from the Holmes paper. In over 200 patients -- and they knew that the first thing that happened is patients get a prodrome.

That's an early symptom.

And that symptom, whether it's tingling, burning, itching -- it varies -- that's the warning signal to get out of the sun. And that -- once you're burned the very first time, the patients have an inherent inborne -- it's psychological avoidance of sun and light.

And all they can think about is how to stay out of the sun. And that's the whole clue to this disease because the minute they stay beyond the warning signal, they burn. And they are laid up, and they lose their time from work. They lose their time from school. They suffer tremendous pain.

(Applause.)

DR. DESNICK: I don't think that came across this morning because I don't think patients are suffering when they're not exposed to the sun. I think the patients avoid the sun so they don't have to suffer. And I think how much time -- can spend in the sun without pain.

Pain is the issue, and you want to avoid it. And I think that's what we really have to understand

first about the disease. And I think the applause that I got means that you all agree. And I think that's the key to understanding how to do the rest, how to define the endpoints.

The second thing is trial population. Well, the FDA tells you. You start with adults. Sometimes you can go 16, age of consent. And once you get something approved, there's -- you can go to a pediatric population.

Being a pediatrician, I know about ages and so forth where kids can do it. At Sinai, we've carried out a lot of clinical trials with young people or we have used approved drugs in young children. And there's probably an age, four to six, in which you can get some reliable cooperation. And after that, you know, you have to think through because individual kids are more mature, some than others.

And then, the endpoints to me are very clear. And I think that we can sit down and talk about what an endpoint is for an adult who can actually write a diary, who can carry out and look at the day and know what they're going to do.

And then again, with this disease, it becomes a huge challenge. And the challenge is to ask people to go out in the sun to get pain. It's almost unethical because --

(Applause.)

DR. DESNICK: And how can you ask placebo patients to do that?

So -- and then we have to think about endpoints. Well, if it's a drug or a treatment that is going to focus on the primary enzymatic defect, that's one thing. If it's going to focus on lowering the proto levels, that's another thing.

We don't have a treatment like that yet. I think they'll come in the future, and we'll have more targeted therapy. But at this moment, we don't have the laboratory measurements that can be made that will -- we know how to do them. But until some treatment comes along that focuses on either the substrate or replacing the defective enzyme or stimulating it, we don't have that choice.

And in fact, what we're doing right now is we're trying different sunscreens, beta-carotene, this

and that, and trying to increase pigmentation. And that's the only thing that we've seen so far that gives us any evidence of, you know, more time in the sun. And I don't say it. We were investigators, but you know it. So I think it becomes very complex.

And I'll just turn to one other quick thing, and that's children. It is extremely hard, as any parent can tell you, to have reliable reporting in a diary or anything like that of your child. And even you forget. And I think that there are plenty of studies that bear that out, whether you're doing diary or whatever.

So -- and I think that the other kind of objective, I know that one thing that we thought might be very objective in the beginning we've learned wasn't. Maybe Maureen Poh will talk about it, but that's photo-provocation where you're paining the patient to know how long it takes to burn. And it turned out just to be too variable. And Maureen studied it, and maybe she'll comment on it.

But I think these are the issues. And I must say I'm awed by Dr. Minder, who went through and

talked about all the challenges here. This is one of the toughest diseases to come up with a viable trial design and endpoints that will really prove it other than quality of life and time in the sun. I just don't know any others. And to me, those are ones that we've learned over a dozen years of working with one particular drug.

Now, when more targeted therapies come that aren't just increasing pigmentation, although that's a novel way of doing it, then maybe we can measure proto -- maybe we can measure efficacy (ph), et cetera.

DR. EGGERS: So there's a lot to unpack in there. So let's work on the thing that the most of you did, and let's follow up and build on what Dr. Desnick said, the balance between choosing endpoints that are meaningful to patients -- the balance and the challenges with choosing endpoints that can be reliably measured and interpreted.

Anyone else on the panel want to build on those comments?

Go ahead, and then we'll go to Manisha.

DR. MINDER: Okay. I said my opinion, and

confirmed with what Bob Desnick said. That is we have a decade of experience to measure efficacy in EPP. And I think we just come to the same conclusion as Bob Desnick did.

DR. EGGERS: Okay. Would you like to …

DR. BALWANI: I have to agree with Dr. Minder and Dr. Desnick. You know, we've been working with clinical trials in this patient population for a while, and we've thought about this extensively.

And we've all come to the same conclusion, that we need a patient-reported outcome, and it's pain-free sun exposure. Improvement in quality of life is also an additional outcome, but I think we need to hear what the patients want and that is the ability to spend more time in the sun so they could have a more normal life.

DR. EGGERS: Okay.

MR. LEE: I agree with what has been said. I think for the provocation, I'm sure Maureen will talk more. It has been -- at least in photobiology world, has been very agreeable for any type of porphyria patients. This -- the results have not been

very consistent.

With other forms of photosensitivity, we can use UV to measure the redness on the skin. But with porphyria you're looking for pain, and it's very, very unreliable in terms of -- very inconsistent in terms of the result. So I think patient-reported outcome is still the best measure for this.

DR. EGGERS: Okay. Go ahead.

DR. TENG: I agree with everyone said. And I think -- honestly, I'm actually having trouble to pick out A, B, C, D, E because there -- well, A, B, C, D, and they're so interrelated.

Just like Dr. Desnick talked about, if we don't know the natural history of this disease and understand the intermittent nature and the episodic nature of this disease in this condition and the pain and taking the quality of the discomfort that you all experience, whether it's burning, itching and pain, they all vary. And it's going to be very difficult to define these clinical endpoint. So getting a really good natural history is very, very important.

The only thing that I want to add on to the

panel discussion is about defining the disease population and stratify the patient population.

And you know, we think about a lot of the genetic disease that over the years there's so many expert here can talk about the disease and the mechanism itself, with the new technology, again, that we develop a new understanding about the molecular biology of the disease and perhaps that, you know, it's time to rethink of the disease, to try to stratify it based on what we know about medically and not report of the clinical symptoms, but based on more objective evidence of, you know -- for instance, like the enzyme activity of the protein and the genetic mutation underlying the disease and the protoporphyrin level, the biochemical certain serum markers and biomedical markers to define the disease a little better in order to stratify this population.

Maybe we'll understand the disease a little sooner. Just like in cancer biology, you know, it's difficult to treat every single melanoma patient the exact same way, and there's some common pathways. But they're also very, very different.

So develop these tools to better define the population and the diseases that we're studying I think is extremely important as well.

DR. BALWANI: I think it's very difficult to have risk stratification in this disorder. It's very well recognized that genetic disorders present across a spectrum. So we want to be able to develop a treatment which can address patients across a disease spectrum, not just stratify and develop disorders for those at highest risk.

DR. TENG: Exactly. I agree. I think that there needs to be that balance, you know, targeted therapy versus a broad treatment for symptomatic and clinical improvement. Yeah.

DR. DESNICK: We've looked at -- we've genotyped over 250 people with EPP. It's a cortisomal recessive disease. We've also looked and published on XLP, which is a very rare form of X-linked, you know, erythropoietic porphyria. It manifests probably a little more severe but in males because it's X-linked.

But to make a long story short, we've never been able to correlate anything other than proto

levels with severity. It's not about the mutations. It's not about the low expression wheel. It's probably 25,000 other genes that relate to the production of protoporphyrin or its stability or its entrance in and out of the mitochondria, or whatever.

So we don't really understand severity in this disease. We know that with every genetic disease, there is a range of variability. Some people burn in two minutes, and some people burn in more than a half an hour. And that's just the tingling prodrome we're talking about, not the extensive pain.

So I think it's very hard to try and strategize anyway. We want to develop a drug that's good for every single patient.

DR. EGGERS: So Maureen, did you want to make a comment? And then we'll -- I think we're just making -- we're going to be weaving a lot in a pretty organic conversation here.

DR. POH-FITZPATRICK: Well, protoporphyria, I think I would agree with my colleagues, is a disorder with a great deal of natural variability. There's a lot of difference in protoporphyrin levels

and pigmentation of the skin and thickness of the stratum corneum and latitude at which you live and whether it's a rainy season or whether you're ambient humidity tends to be dry. There are a lot of variations -- whether you're a person who likes to be outdoors, doesn't like to be outdoors.

What we do know as much as we can about some quantifiable value related to the pain or reaction that's gotten -- I would agree with Dr. Desnick -- is that there is some relationship between a very low porphyrin level and a very high porphyrin level and the likelihood that you'll have lesser photosensitivity or greater photosensitivity.

But it's not a mathematical kind of relationship. There are all these other variables that weigh in so much that it's very, very difficult to control for all those confounding variables and designing any mathematically defined outcome.

DR. EGGERS: Okay.

DR. POH-FITZPATRICK: So what I think I've heard this morning from so many of the patients here is that they know very well what their problem is.

And if you listen to many of them, you can really get the same story pretty much.

It's the pain. It's that deep pain. It's the unremitting pain. It's the pain that's indescribable because there's no language equivalent to it. And then you hear stories about, well, we did this drug or that drug or whatever. And we know that we were doing better.

With all these variables and ages and pigmentations and latitudes and whatever, that is the criterion that I think is the most compelling, is that these folks know when they're doing well and when they're not.

And they have a whole construct of what they have to do to get them to be able to sort of live. They're alive. They've very alive. They're here, but their lives are so constricted and so constrained by all this stuff that it's really important, I think, for all of us to try to think together on a way of getting them so they can lead a life that's worth living to the extent that most of us can lead a life that's worth living.

So what can we do about that? Well, we can try to do the best we can with these clinical trials. There have been several of them now. I think the endpoints are kind of vague, at best, except for the big criterion, is do the people who have done it believe convincingly to those who listen to them that there is a difference when they're using whatever method they're using to relieve this pain. And I think that's the best criterion that I can listen to.

DR. EGGERS: Okay. Yes. Go ahead.

(Applause.)

DR. MARCUS: So --

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. MARCUS: Can -- yes, listening to the patients is very important. And you know, as a regulator, I'm still trying to quantify it.

And I would just like to acknowledge that -- you know, I believe you talked about the heterogeneity of the disease. And I believe Michael has 1 minute, and other people may have slightly more than 20 minutes.

So please understand from the perspective of a regulator, for a product that gives you an additional five minutes in the sun, that will be transformative for Michael, who has one minute. That will actually be a difficult difference to measure in somebody who's got over 20 minutes.

But we need to figure out a way that we can measure the impact for both people. And this is where -- yes, we can listen to the patients. But in the end, we're regulators, and we have regulations. And we also have to try and design a clinical trial that can convincingly demonstrate an impact such that we can take an action.

And so I'm saying that, in order that you understand, I believe we should be listening to you. I'm just helping -- trying to help us have a dialogue in a language and in a manner that we can all come away with what we need, all of us.

Does that make sense to people? No?

(Crosstalk.)

UNINDENTIFIED MALE SPEAKER 9: All of our levels aren't the same all the time. Our porphyrin

levels are different. The UV lights are different. The outside index is different.

DR. MARCUS: Right. So this is challenging. So this is a challenging conversation to have. So one thought that I'm having in having this dialogue today -- and I'm going to say all this, and I cringe a little because my patient reported outcomes colleague on the end of the table, Dr. Papadopoulos, may cringe when I start throwing this stuff out because patient -- you know, there is a method to patient-reported outcomes.

But for me, if -- you know, in just talking to people today and having read your -- you know, the letters that I've gotten, you know, if you start out with a list of activities that range from walking from my house to the mailbox, walking from my car to a store, driving to work, taking my child to the park, watching a one-hour soccer game, those are increments of time that are meaningful to you.

And so it may be meaningful for one patient to go from being able to walk to the mailbox to being able to walk from the car to the store or being able

to drive to work. Those are meaningful incremental benefits to you that aren't necessarily -- that are more meaningful, frankly, to me than a five-minute incremental benefit because it speaks to the quality of life gained for you. And I understand very small increments of ability to tolerate the sun translate into huge quality-of-life changes for you.

But we need to be able to -- and this is I think where we're all struggling. I -- we hear you, but we need to be able to put that on paper. And to me, just talking about those activities is very clear. But we've been measuring minutes -- you know, small minutes of benefit, and that's much harder. And maybe I just need to tell you that. That's much harder than actually just saying I can walk from the car to the store now. But we have to measure that even in a systematic way in order to be able to demonstrate efficacy.

So I've gone on for too long.

DR. POH-FITZPATRICK: Let me just add about photo-provocation testing, which was a question. Having tried to do it in protoporphyria patients with

a fairly good understanding of the natural history of the disease and photobiology and wavelengths of light and machinery and filters and so forth and so on, I found it to be extraordinarily difficult, almost uninterpretable, in the long run. So I would tend to lean away from trying to use that as a quantitative criterion for all of the variable confounding factors that were described.

If some way could be a measure developed as you're suggested to determine the impact factor on individuals' improvement with or without any treatment, that could be mathematically, statistically analyzed in such a way that you could get some kind of a semi-quantitative number to quantify the impact on 100 different, 200 different patients, considering what their ordinary baseline value would be and then after the treatment or during the treatment, what that impact factor turned out to be. And that would be up to the statistical experts to design that query.

DR. EGGERS: We'll let -- okay. Elisabeth, please.

DR. MINDER: I do not agree. I think the

variability is so large between these and the patient also has a priming phenomen (ph). And we have so many influences we cannot control for them.

But I think what is best is integral to what we have measured in the Phase III trial. That is a total number of sun exposure without pain. There you have a statistical significance difference between the patient on placebo and those on active. And I think if you look at that, that it's much better than any average on day. But you cannot use it an average on day because on average on day it's subject to a lot of variation.

But if you take the integral for four months or six months so you have probably a rather adequate measurement because the variation say are equally distributed during this time. And so we have a statistically significant effect in the U.S. trial.

It -- the patient increased their time in the sun without pain for, I think, one-third or one-half. So they have a really strong increase in the sun exposure time. And I think this is just what translates. Also variation -- and I think that the

best measurement we have. We will not find anything which is better than that.

(Applause.)

DR. BEITZ: Dr. Minder, if I could follow on to understand a little bit better, you've presented information about pain-free time in the sun. There's a challenge, as has been expressed not only by the patients, but also by the experts in their presentations with the variability of the disease.

You've mentioned yourself, or perhaps others, the seasonality to the disease. Some have mentioned -- and I'm going somewhere with all these caveats and rambling. There is going to be a question.

Some have mentioned -- Dr. Desnick, I believe -- that there may be a correlation between porphyrin or protoporphyrin levels and disease severity. Those can vary from patient to patient. Are there -- were we hypothetically to use time -- what was it -- time -- pain-free time in the sun, were we to look at that as an endpoint, are there other things that we should control, maybe not formally

stratify -- possibly stratify for or analyze for?

Does the design need to take into account season unless you're doing a full-year trial? Does the design need to stratify or analyze based on baseline porphyrin levels? Are there -- help us with other things that may, whether that endpoint or a different endpoint, are there things that we can do in the trial or in the analyses that could help us.

DR. MARCUS: I just want to make one more comment in this conversation. And I get the sense that the conversation we're having is that you're saying we have statistical significance. And what we're saying is help us come up with clinical trial designs moving forward.

So I don't want to imply in any way that we are ignoring the findings of alfamelanotide trial. I do want us to focus on forward thinking so that we are convincingly able to demonstrate an impact on -- for example, my goal would be in a rare disease. You know, what can we show with 10 patients? What can we show with 20 patients?

We need -- I think we can -- I'm not willing

to say we've got the best endpoint that we're going to have, but that's me. I don't want to stop at one solution, and as I've mentioned already --

UNIDENTIFIED MALE SPEAKER 6: The first step.

DR. MARCUS: What's that?

UNIDENTIFIED MALE SPEAKER 6: It can be the first step.

DR. MARCUS: Absolutely, and I'm not saying that it's not. But I'm trying to have a broad conversation.

UNIDENTIFIED MALE SPEAKER 6: (inaudible - off mic).

DR. MARCUS: Right.

UNIDENTIFIED FEMALE SPEAKER: You can't prevent bullying? I mean, that's what we feel like. I mean, have you ever been out there and been bullied as an adult or as a child --

DR. MARCUS: I -- we should -- I understand, and I --

DR. EGGERS: The microphones.

DR. MARCUS: I'm really trying to use this

time to help us think about clinical trials. This is not a statement about any -- the state of any drug development program by wanting to be forward thinking. It's not commentary on what's been done already. That's all. And that's really all I can say.

But I just -- I think that there has to be a certain amount of -- I don't know a better way to say it, and I -- believe me, I understand the frustration. I understand your suffering.

I can't truly understand it because I haven't lived through what you all have lived through. I can certainly --

UNIDENTIFIED FEMALE SPEAKER: You have to pass it on to a child.

DR. MARCUS: I understand all that. I mean, I hear you. But we're really trying to focus on -- as I said, pediatric clinical trials in this disease, which is already rare, might be a trial where you've got 5 patients, maybe 10 patients. And what can you do to convincingly demonstrate an impact and determine a safe dose?

And so I think we can do better than pain-

free time in the sun. We've already talked about all the complexities and variability in patients. And it seems to me an activity is fairly easy to demonstrate.

Just one that's come up today of being able to walk from a car to a store. I think that's a significant impact. I think that might be something that's readily measured in 5 to 10 patients. But I -- again, I cringe when I say that because this is a collaborative effort with everybody in the room.

I'm thinking about paths forward, and that's where I -- you know, I've already thought about ways that this can be done. And I really would like some help, and that's what you're here for.

(Applause.)

DR. MARCUS: And I'll just say one last time this is not commentary on anything that's already transpired.

I've been the division director of this division for two years, and I'm bringing a new perspective to our division. And I'm trying to accomplish many tasks simultaneously, and this is one of them, trying to create paths forward. And it would

be great if we could all work on that.

DR. EGGERS: So then just as the moderator, do we want -- do you still want your -- Jill, do we want to go to your question or move on?

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. EGGERS: Okay. Then you can respond. What comes to mind when you're hearing this?

DR. DESNICK: You know, I would also like to see better endpoints -- endpoints that are more robust, endpoints that really are convincing.

The problem is twofold. If you're measuring viral load and protease inhibitors, you've got laboratory data that you can really measure. In this disease, you -- we don't have a target of proto because the proto levels didn't change in any of the studies. And we don't have a target of measuring increased enzyme activity. These are the two basic path -- this is the basic path of physiology of why they have this disease.

And until we have targets like that, I don't think, because of the inherent nature of the disease

and the fear of having pain, that we're going to be able to develop the kind of robust measures you want.

In fact, if you look at the data from the trial that we did do, both European and U.S., we found that most of the patients, whether they were in the placebo group or they were in the treated group, still feared going out in the sun. And that's why the measurements that we got were so low.

And that's why the differences are not robust because nobody wanted to get burned. They have this inherent fear so ingrained from the first time they -- who got laid up from being burned when they were a kid that all they do all day is work a schedule, as you heard Dr. Poh say, to make sure they can get through the day without getting burned. And I think that's the inherent problem because most of us at this table have thought how do we do it better. How would we do it better?

At first, we thought maybe it was photo-provocation. But then we learned that it's like radiation, that you build up a level. And if you come on your bike or you get exposed to the sun and you get

a baseline level that's elevated, it's different from time to time. And that's too variable. It doesn't allow for any objective measurement.

When we talk about other ways of doing it, there isn't a device that would allow people to wear it, like a child, and go around and measure the intensity, the wind, the weather, the humidity, all these kinds of things, and integrate that into chill factor, if you will, or a pain factor. And I think until we have such instruments, it's going to be very hard to do this.

And I think we all struggle with the exact same question you're answering, and I wish that we could come up with a better -- I'm not wed to any particular trial endpoint. If there was something better, we should try it. But until somebody really comes up, I don't know.

And I will tell you that in the study that we did do, the small amount of difference that we saw was, in Europe, significant. In the U.S., it was .04. And that doesn't reach -- that's -- you know, that's great, but it's not what you'd like, like .001. And

that would be convincing.

And I think that until we can think of a better way -- and if you have some ideas, you should share them with us because we've dealt with these patients. And the patients are all here, and maybe we can work out something together.

I really worry about how we can get these kids into a small trial, like you suggest, that will be meaningful and allow you to do more than safety.

And that -- and the only other thing that is convincing to me, I must say, is that there are people here who have gone three to six times to see Dr. Minder. There are people in Italy and Belgium and Switzerland, the report of Minder with 107 patients where there was very little -- you know, if they got pregnant, they stopped for a while. If they came for a long distance or whatever it was that they couldn't do or if they had to be at work, they were -- you know, they didn't get the drug. But the rest of them have been on drug continuously for --

DR. MINDER: For up to eight years.

DR. DESNICK: -- up to eight years. And to

me, that -- you know, being a physician, when somebody comes back and back and back, it must be doing something meaningful because it's an effort.

DR. LINDSTROM: Thank you so much. You've raised a lot.

And I want to move away from the results of a particular trial to a question that has come up, in my mind. And I'd love to hear how you utilize laboratory measures in your care of patients.

So protoporphyrin measures, are those something that are -- that you measure and follow? And again, don't read anything into this. My question -- I'm -- it's a question. I want to know how you use those levels.

And then I have a separate question. In fact, I'm going to lay it out here, but maybe you can address one fully and then address the second. I'd also like to hear from you because we have this unique talent pool right now.

I'd like to understand. People have said that photo-provocation doesn't work. And I'd like to hear a little bit more about that with regard to --

and you mentioned a UV device, almost like a radiometer that folks wear to measure, you know, X of radiation and so forth.

But my question comes from both of those. I believe it was Dr. Minder, perhaps Dr. Lim, mentioned that there may be multiple wavelengths involved, the short band, the higher visible lights. UV may be provoking in some subsets of the patients.

In light of the potential variability in -- or potential spectrum of wavelengths that may be involved, can you also speak to how that might impact photo-provocation, positively or negatively, whether it could be used and whether -- how that would impact monitoring devices? The first question is more important.

DR. EGGERS: So before you get to those two questions, just a time check. Do we have open public comment signup?

MS. CHALASANI: We do.

DR. EGGERS: Okay.

MS. CHALASANI: The full 10 minutes.

DR. EGGERS: The full 10 minutes. Okay. So

we have then another, we'll say, 10 minutes to have this facilitated discussion. So maybe briefly answer Jill's two questions, and then we'll ask for one final question.

DR. LINDSTROM: First, monitoring use of porphyrin levels in your -- clinically.

DR. BALWANI: I can respond to that. So as part of our consortium, we try to develop guidelines for monitoring patients. And we do monitor protoporphyrin levels annually. We find that it often doesn't correlate very well because there is some variability in protoporphyrin over time.

But we do like to monitor them longitudinally to see if there's an indicator. For instance, if we would see a significant jump in the protoporphyrin level, we would certainly be concerned about liver disease.

Some of the other parameters we measure are hemoglobin, hematocrit. We measure your iron profile. We measure vitamin D levels, liver function tests for patients. So those are our standard monitoring annually for all of these patients.

And I'll let Dr. Poh-Fitzpatrick or Dr. Minder talk about photo-provocation.

DR. POH-FITZPATRICK: Okay, I will. I agree with Dr. Balwani. That's how laboratory standard tests are used in monitoring patients with protoporphyria, chiefly looking for changes in the protoporphyrin level going higher, which would suggest then you were having a liver problem, looking at the liver function tests to see whether or not that is borne out, you know, pursuing liver studies and so forth.

Plasma porphyrin may be going up. Stool porphyrin may be going down. And that's understanding the natural history of the disease and using these parameters in a clinical sense to take care of each individual patient.

We almost never use photo-provocation testing in normal clinical work. This is only a research type of procedure. And I understand that some photo-provocation testing was done on areas that have been light exposed chronically over time and probably have been exposed to light coming and going

and over the last week -- was it rainy, was it sunny, whatever -- which would have put a very large variable factor load on any result that you might get.

Using photo-provocation on an area that's more sun protected would be a better risk. But still having done that, I can tell you that it may be very, very difficult to reliably do it reproducibly day after day after day, even under the best of circumstances. So we generally don't use it much for anything, really.

DR. LINDSTROM: Would any of you see any merit to stratifying by protoporphyrin levels?

DR. POH-FITZPATRICK: In the sense that you could probably expect that individuals who have a lower protoporphyrin level toward the lower end of the spectrum, someone who has a level that tends to run around 300, maybe some 250. Maybe someday it's 400 -- somewhere around there would probably be less photosensitive on average than an individual whose protoporphyrin level tended to vary between 3,000, 2,500 and 4,000. They would probably be much more photosensitive.

But on the other hand, one might have a whole lot more pigment and have some natural protection. So there are many things that would factor into what you can use, changes in protoporphyrin levels to predict about level of photosensitivity.

And then all the other confounding variables -- what's their life like? Do they go out? Don't they go out? What's it like where they live? Do they -- you know, there's just so many things to try to control for that I think it's virtually impossible.

Going forward and testing new things coming down the pipeline, looking at things like protoporphyrin levels, if there is something that actually does change the protoporphyrin level by either affecting the pathway, facilitating conversion to protoporphyrin, fixing the enzyme somehow and giving the new enzyme, doing things that would actually change the dynamic equilibrium of protoporphyrin manufacturer circulation and excretion, there you could use those kind of numbers as endpoints, understanding that there's going to be a

certain variability that you just have to factor in.

DR. LINDSTROM: Of course.

DR. MINDER: So just can I say something?

DR. LINDSTROM: Thank you.

DR. MINDER: We have a continuous distribution in the protoporphyrin levels. It's some skewness. It's not a symmetric distribution, but it's a continuous. We don't have subgroups, which we could identify.

And we have no connection with genetics. In Switzerland, we have a relatively homogenous population, so we have repeated the same mutation. and we could not find any correlation to the mutation. So it's just -- we don't have subgroups. And we don't -- also, we don't have subgroups in the clinical symptoms.

It's really continuous. We have patients who have less symptoms, but it's -- we cannot -- a group is less symptoms. A group is high symptoms. It's just a continuous between low and high symptoms. So -- and we cannot identify. Protoporphyrin has some effect, but it's not the effect, what we find.

DR. EGGERS: We're going to go with Dr. Balwani, then Dr. Lim real quickly. and then Dr. Beitz has a final question.

DR. BALWANI: So just again to reinforce what everyone said, in our analysis of our patients in the Porphyria Consortium, we have about -- data on 226 patients. And we did see a correlation with protoporphyrin levels and time to bond.

It's the first time we were actually seeing a correlation with high protoporphyrin-level patients having more severe symptoms. Again, there are a lot of caveats to this, as Dr. Poh-Fitzpatrick discussed.

DR. DESNICK: If you look at the data from that study that we don't want to talk too much about, the ones --

(Applause.)

DR. DESNICK: -- please --

(Applause.)

DR. DESNICK: -- the ones that had the most effect, the longest in the sun, it was almost curative for them because they almost normalized. And they were the mildest patients.

So when you start thinking about which way you're going to go, if you're going to pick the most severe, they may get X amount of benefit whereas the others are going to get even more. And I think one has to think through. We don't want to label with any EPP drug that says your protoporphyrin level has to be X. And that's why I think most of us feel that looking at the whole population is the right way rather than --

(Applause.)

(Crosstalk.)

DR. POH-FITZPATRICK: The intent was stratification, not label.

DR. MARCUS: Right, stratification as a means of controlling for that confounding variable in order to better demonstrate the treatment effect.

And I guess I'm willing, again, in terms of I understand that traveling, you know, one of the factors that patients reported as important is whether participation in the clinical trial would require travel. I understand that there can be cost and travel constraints to participating.

And so if we can identify a subpopulation -- you know, if a trial can be enriched with the population, as you said, actually the milder patients who have a more dramatic effect, it may take fewer patients to meaningfully demonstrate benefit.

And you know, labels describe the clinical trials under which a product is studied. You know, I think it would be upon us to discuss whether a subpopulation can adequately demonstrate benefit across all of the population and make that extrapolation for an indication, describing the clinical trial in the label, you know, that was used to demonstrate that.

DR. EGGERS: Dr. Lim, did you want to say something?

DR. LIM: Yes, just a brief comment about the photo-provocation testing. The action spectrum of porphyrin is in a visible light range that measure four from 400 on up. Up to now, there had been very, very few light sources that contains only pure visible light.

There are now light sources that can be used

that contain only pure visible light. We have done a number of studies on that, not for porphyria. But -- so theoretically, there would be one that can be used. But again, we don't have any data right now.

And those light sources right now, the irradiation field is still very, very small. So if we need to do that, we have to modify to see if we can irradiate a large area to try to reproduce the symptoms. But again, I just do not have any data on that.

DR. EGGERS: So I'm going to -- just for the sake of time, I know some people have to travel at 4:00 o'clock. Then the last panel question will come from Dr. Beitz to be answered. And then we're going to move into the public comment session.

DR. BEITZ: No, just a question about extrapolating efficacy from adults to children. I was wondering what your thoughts were. If you had a treatment that was efficacious in a 25-year-old, what are your thoughts about saying anything regarding efficacy of that same product in a 5-year-old or a 12-year-old? Do you think it's realistic that we could

extrapolate the experience in older individuals down to younger?

DR. EGGERS: Why don't we start with --

DR. BEITZ: This is for efficacy now.

DR. EGGERS: Dr. Balwani, do you want to -- okay.

Dr. Minder?

DR. MINDER: Actually, as of genetics, it's about the same in the children less (ph), and as in all of (ph) I don't see a difference. So I don't see that there should be -- that there is any -- speaks anything against to extrapolate. I think children have usually, in my experience -- I'm interested what my colleagues say, but children usually have a little bit lower protoporphyrin levels.

And the protoporphyrin levels increase during puberty. But on the other hand, the children have very thin skin. So they are also very sensitive. So I think this balance for the lower protoporphyrin level. So I think children may react really the same as adults on the drug.

DR. EGGERS: Add on that, Dr. Balwani?

DR. BALWANI: Yeah, I would agree with that. I don't see any reason we cannot extrapolate the results from adults to children. I do think children will get a benefit.

DR. EGGERS: Okay.

(Applause.)

DR. BALWANI: And I just also wanted to mention that it would be great to have good quality of life indicators in the pediatric population. I think we are really lacking that, and that's a very significant point to capture.

DR. EGGERS: Final comment? Or Dr. -- two final comments.

DR. POH-FITZPATRICK: Okay. Well, I would just say that in having treated quite a number of pediatric patients with protoporphyria, their skin is indeed are probably somewhat thinner. Their protoporphyrin levels varied all over the place just the same as adults.

They -- the impact on their lives is probably even greater than that on adults, who the parents do a wonderful job of trying to make a life

for them. But I think anything that we can do to make more -- to expedite any arrangements for being able to translate an agent that is approved in adults to the pediatric population, particularly with this disorder, which is so devastating to childhood, would probably be a worthwhile thing to do.

And the flexibility and judgment that is accorded to the FDA by statute would seem to be great criteria to apply in this situation.

(Applause.)

DR. EGGERS: Dr. Teng, did you have a final comment?

DR. TENG: I'm just commenting on -- along the same line that for children, that besides, you know, the regular stuff that we all appreciate other things like attention deficit in school performances and just some of the psychiatric impact. It can probably be considered into some of these endpoint measurement as well.

Other things that a couple of people in the audience have pointed out that, you know, for instance, a bone fracture, risk of fracture and bone

density, you know, questions that we may not know at this point. So those are the things, and maybe, you know, can be quantifiable and, you know, their vitamin D and the calcium and all that.

DR. EGGERS: Okay. So with that, we're going to close the scientific portion.

A couple things -- please leave your clickers on the table. We've had people think of them as souvenirs before, but please leave them on the table.

This discussion has opened up a number of complexities. There's still the public docket. We didn't get to go out in the audience and ask for patient comments on much. You managed to give your thinking, I think, very well through the applause of the various comments that were made by the experts up here.

But we do -- if you have thoughts on clinical development or clinical trial design, please share those with them because, even though it wasn't said out in a public forum like this, the comments are all coming to us and they are important. We want to

hear your perspective for that.

Evaluation forms -- please fill them out and let us know how we're doing. We learn something every time, and we use the feedback we get to make our meetings better.

So with that, I'm going to turn it over to Pujita Vaidya.

MS. VAIDYA: Hello everyone. I'd like to thank you all for coming today. We've had very rich discussions, and now we're moving into the open public comment session.

I just wanted to let you know that we will not be responding to your comments, but they will be transcribed and be part of the public record.

So we have 7 people who have signed up, and we have 10 minutes for each person -- for the whole session. So each person will get a minute and a half.

So what I've done here is the light -- this will turn on when your minute and a half starts. When it turns yellow, it will -- you will have 30 seconds left. And then once its red -- I would like to apologize right now -- I will need to ask you to

please stop, and then we'll have to move on to the next speaker.

So I'll run through the order of speakers. If you could all line up right up here on the right. We have set up a mic over here. And then we can get started. So first, we will have Michael Olscher, sorry. We have -- and I apologize in advance if I mispronounce your name.

We have -- next, we have Desiree. Then we have Olivia Donahue (sic), Vickie Lewis, Julianna Amodei, David Garrett. And then finally, we have Jasmin Barman. Sorry, if I mispronounce your name. Okay.

UNIDENTIFIED MALE SPEAKER: Jasmin.

MS. VAIDYA: Oh, Jasmin. Yes, Jasmin Barman. Sorry.

Okay. So now we can get started. So first, we have Michael.

MR. OLSCHER: The day's been informative for you. I just want to stress that what a difference even five minutes would make to my life as far as walking with my head up from a car to a bank, not

worried about what people might be thinking or having the police called on me just because I've got a hoodie on and I look suspicious. That would be just drastic for me, to be able to walk anywhere really and hold my head high instead of looking down.

And lastly, I basically just want to address the younger people and the children and let them know it does get better. It does get easier. People will bully you no matter what. I think if you're different, they'll pick on you.

So you have one life. Do what you can. If you can cover up and that works for you and you're worried about what other people think, don't. Just cover up. Get out there. Enjoy life no matter what happens with drugs. I try not to get my hopes up, so you just deal.

So don't let it hold you back. If you can, get out there. Ignore what everybody says about you because, really, it's your experiences that matter. So go live your life. That's all. And thank you.

(Applause.)

MS. VAIDYA: Thank you, Michael.

Next, we have Desiree.

DESIREE: Thank you again for this opportunity. I know all of us are grateful. I'd like to speak for the patients who had to work and couldn't be here and who couldn't be on the web today. And they would have me say to remember these things.

First off, many of them told me that when they did the trials, the clinical trials for alfamelanotide, some of them waited until they were halfway through to even test it. It took them that long to step their foot out the door. They were thinking about it.

Secondly, they said to remember that fear is a great motivator. Love is the greatest motivator, and I think it's love for these children and love for one another is why so many people came, not just for themselves but for one another. But fear is a great motivator, and that fear is very prevalent in everyone, as you have heard.

And in designing a trial, of course, we're hoping that you're talking about another trial and not repeating the trials that we've already done because

they expressed they wouldn't be willing to do that. But in new trials and for these children, that is also going to be very important because they are developing this same fear.

MS. VAIDYA: Thank you, Desiree.

(Applause.)

DR. EGGERS: Next, we have Olivia.

MS. DONAGHY: Hi. I'm -- my name is Olivia, and I'm 10 years old.

I just wanted to say that the pain is worse than anything you've ever felt. There's no word to describe it. You will do -- with EPP, you will do anything you can to get away -- to avoid the pain.

When I was four and I was having one of my first reactions before I was diagnosed, I -- in my sleep, I was banging my hands against the wall because it felt better. So also, I'm guilty because my brother loves to go outside and play. And I'd love to join him, but I can't.

(Applause.)

MS. VAIDYA: Thank you.

Next, we have Vickie. Yeah, come on Vickie.

Oh, you can come on up.

MS. AMODEI: Hi. I'm Julianna Marie Amodei, and I'm 11 years old. I'm from Syracuse, New York, and it took until last year for me to get diagnosed with EPP.

During the last six years, we have -- we had to leave many family vacations due to a reaction. We have been to many different specialists. My mom saw the Dateline show, and she asked the dermatologist to order a blood test for EPP. And my hands and feet, they burn and sting. And my nose gets really patchy whenever I'm having a reaction.

And whenever I want to go out to outdoor camps or sports, I have to say no. But I think that with Scenesse, I could say yes.

(Applause.)

MS. VAIDYA: Thank you, Juliana.

And then next we have Vickie -- Vickie Lewis. Okay.

Okay. So we'll move on to David Garrett.

MR. GARRETT: Hi. I'm David Garrett. My birthday was yesterday, and I'm older than 10 now.

(Laughter.)

MR. GARRETT: I just wanted -- and it goes more to the trial. In passing, it was mentioned a minute ago about vitamin D levels. As it happened, when I was in the Stage 2 -- the Phase II trial and had the active drug, I overlapped twice with my regular doctor and checking my blood. And she was surprised because I actually had higher -- much higher than for me and higher than the midrange of vitamin D.

Since then, I'm now up to 10,000 IU a day just to keep it at the minimum level. It might be something you can look at because all of us, we don't get sunshine at all. We just -- there's no way to go the simple way.

And I actually had a visiting doctor one time comment on my vitamin D and say, well, this is simple. Just go outside every day for 25 minutes --

(Laughter.)

MR. GARRETT: -- without sunscreen, and you'll be better. You'll feel better.

The second thing is I did the trial, and it wasn't a matter of even just hours a day. It was the

whole day that I could be in the sun. I had maybe one time at the end of the trial on the very end of the pellet where I was slightly burned.

I really want a BMW convertible before I die.

(Laughter.)

MR. GARRETT: You're really in the way, and you're stopping that. So if you could step it up before I go away so I can buy it.

(Laughter.)

(Applause.)

MS. VAIDYA: Thank you so much, David.

And finally, we have Jasmin.

MS. BARMAN: Hello. I just wanted to add two thoughts. One is in the trials, pain-free days really (ph) should. But it's likely an underestimation of the real value because, for us patients, also less pain matters and, also, when the symptoms resolve faster, what we also experienced. That was the first thing.

The second thing is that we heard that it's about clinical trial design for kids. And I just want

to say that we just heard how hard it is to measure the efficacy in adults. Then we heard that it's unethical to put patients, EPP patients, in the situation to expose themselves to this kind of pain.

And we also heard that patients, also kids, discontinue treatments which are unsuccessful. So I can say for myself, I had antihistamine. I had iron therapy. I had beta-carotene. I had sunscreens. I put this in the bin because it wasn't working.

So one suggestion could be to just measure treatment outcomes -- treatment adherence as treatment outcome in kids because it's a special situation.

Thank you.

MS. VAIDYA: Great. Thank you, Jasmin.

(Applause.)

MS. VAIDYA: And finally, we have a quick announcement from Desiree.

DESIREE: Those who are on the bus, I'm sorry, but we're going to have to leave right now --

MS. VAIDYA: Okay.

DESIREE: -- because the bus is leaving.

MS. VAIDYA: Okay.

DESIREE: And please forgive us, but if you're going --

MS. VAIDYA: Okay. We have --

DESIREE: Thank you again very, very much. We sincerely appreciate it.

MS. VAIDYA: Thank you.

We have a quick, final comment from Dr. Marcus, so I'll call her up.

DR. MARCUS: I realize you all have to leave, so I'll just be brief. This has been of tremendous value to me, and I hope that no one walks away today feeling like their efforts have been in vain.

As I opened this morning and I will close now, I really am in awe of you, of the efforts that you went to, to come today and of the incredible challenges that you face on a daily basis to do things that I take for granted.

And I think all of us here have learned a tremendous amount and can use that knowledge to move treatment for this disease forward.

So thank you again, and safe travels.

(Applause.)

(Whereupon, the meeting was concluded at 4:31 p.m.)

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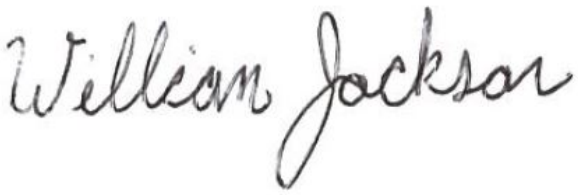

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