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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)  
White Oak Campus  
10903 New Hampshire Ave  
Building 31, the Great Room  
Silver Spring, MD 20903

Reported by: Erick McNair, RPR/CSR,  
Capital Reporting Company

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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

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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

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

2                   Cortney Madden

3                   Michael Ferry

4                   Steve Ferry

5                   Michael Olscher

6                   Sue Ellen Phillips

7                   Jasmin Barman-Aksoezen

8                   Patricia Bestecken

9                   Nanelle Taylor

10                  Paul Hugo

11                  Becky Griffiths

12                  Ginger Honiker

13                  Sue Gore

14                  Kerry Wiles

15                  Victor Mejias

16                  Madeline Harvard

17                  Meghan Rohn

18                  Tim Sanders

19                  Rocio Sanders

20                  Tracy Leach

21                  Jennifer Beck

22                  Cheryl Crites

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

2                   Denise Edwards

3                   Candace Colbert

4                   Kate Sheffield

5                   Shellie Miller

6                   Joe Lewis

7                   Diana Ijames

8                   Rocco Dambro

9                   Olivia Donaghy

10                  Julianna Amodei

11                  Ashley Eskew

12                  Nick Guanciaie

13                  Theresa Lester

14                  Tom Foley

15                  Monica Foley Fleegel

16                  Shawn Willis

17                  Alex Baria

18                  Rachel Wise

19                  Jere Wise

20                  Rob Saupe

21                  Pierre Mouledoux

22                  Hannah Peterson

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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

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## 1 P R O C E E D I N G S

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

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

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

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

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



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

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

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

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

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

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

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

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

1 CDER.

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

5 MS. CHALASANI: Meghana Chalasani.

6 MS. VAIDYA: Pujita Vaidya.

7 MR. THOMPSON: Graham Thompson.

8 DR. EGGERS: And someone else?

9 MS. VAIDYA: We have Laurie (ph) and ...

10 DR. EGGERS: Oh, Laurie?

11 MS. VAIDYA: Yeah.

12 DR. EGGERS: Laurie, raise your hand.

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

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

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

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

1 here.

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

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

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

8 (Laughter.)

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

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

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

15 MR. S. FERRY: Steve Ferry, Virginia.

16 MR. OLSCHER: Michael Olscher, Warkworth,  
17 Ontario.

18 MS. PHILLIPS: Sue Ellen Phillips from  
19 Michigan.

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

22 MS. BESTECHEN: Hi. My name is Patricia

1 Bestechen, and I'm from Dover, Delaware.

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

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

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

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

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

12 MS. WILES: Kerry Wiles, Omaha, Nebraska.

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

15 (Laughter.)

16 MS. HARVARD: Madelyn Harvard, Memphis,  
17 Tennessee.

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

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

22 MS. R. SANDERS: Rocio Sanders from

1 Satellite Beach, Florida.

2 MS. LEACH: Tracy Leach from Pennsylvania.

3 MS. BECK: Jennifer Beck from Connecticut.

4 MS. CRITES: Cheryl Crites from Michigan.

5 MS. EDWARDS: Denise Edwards from Michigan.

6 MS. COLBERT: Candace Colbert, Boston,  
7 Massachusetts.

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

10 MS. MILLER: Shellie Miller, Denver,  
11 Colorado.

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

14 MS. IJAMES: Diana Ijames, Missouri.

15 MR. DAMBRO: Rocco Dambro, Westchester,  
16 Pennsylvania.

17 MS. DONAGHY: Olivia Donaghy, Orlando,  
18 Florida.

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

21 MS. ESKEW: Ashley Eskew, South Carolina.

22 MR. GUANCIALE: Nick Guanciaale from

1 Syracuse, New York.

2 MS. LESTER: Theresa Lester from Southern  
3 Minnesota.

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

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

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

10 MR. BARIA: Alexia Baria, Chicago, Illinois.

11 MS. WISE: Rachel Wise, Philadelphia,  
12 Pennsylvania.

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

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

16 MR. MOULDEDUOX: Pierre Mouldedoux from New  
17 Orleans.

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

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

22 MS. LACHLAN: Lachlan (ph) from Boston,

1 Massachusetts.

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

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

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

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

12 MS. EVANS: Gail Evans, Bowie, Texas.

13 MR. HUSSEY: Tim Hussey, Atlanta, Georgia.

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

17 MS. MORRIS: Barbara Morris from Berlin,  
18 Maryland.

19 MS. BITTNER: Rebecca Bittner from  
20 Philadelphia, Pennsylvania.

21 MR. CRANDALL: John Crandall from  
22 Cincinnati, Ohio.

1 MR. FELTS: Mitchell Felts from Cincinnati,  
2 Ohio.

3 DR. EGGERS: We miss anyone? Wow.

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

6 (Applause.)

7 DR. EGGERS: And we thank you.

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

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

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

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



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

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

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

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

1 afternoon.

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

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

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

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

1           Please feel free to get up at any time. We  
2 don't have any scheduled breaks before our lunch at  
3 12:30, but we encourage you to get up as you need. If  
4 you need to walk around, whatever you need to do,  
5 please feel comfortable. This is an informal meeting  
6 setup.

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

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

16           Oops.

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

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

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

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

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

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

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

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

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

22 So having this kind of dialogue with you is

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

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

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

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

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

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

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

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

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

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

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

12 Thank you.

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

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



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

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

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

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

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

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

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

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

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

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

22 The main reason is a protoporphyrin ESA,

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

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

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

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

1 subjects in their patient population.

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

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

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

1 very familiar to all of you.

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

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

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

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

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

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

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

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

1 spectrum pretty much is filtered out by window glass.

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

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

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

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

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

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

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



1 Red and blue marks can occur.

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

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

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

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

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

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

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

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

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

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

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

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

1 I'll stop here. Thank you.

2 (Applause.)

3 UNIDENTIFIED FEMALE SPEAKER 1: Oh, sorry.

4 I must be pushing the wrong button here.

5 (Side conversation.)

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

8 UNIDENTIFIED FEMALE SPEAKER 1: Okay.

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

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

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

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

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

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

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

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

1 describe your symptoms or your effects, for example.

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

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

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

19           So that is an overview of the discussion.

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

21           UNIDENTIFIED FEMALE SPEAKER: (inaudible -  
22 off mic).

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

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

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

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

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

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

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

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

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

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

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

16 DR. MARCUS: Oh, okay. Yeah.

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

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

22 DR. EGGERS: That would be great. Yes.



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

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

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

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

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

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

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

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

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

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

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

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

22           So the list underneath here is what we do

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

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

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

21           And I've been taking care of a teenagers at  
22 12 years old. At 10 years of age, they already have

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

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

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

1 work.

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

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

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

1 protective measures are also very important.

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

7 So the  $\alpha$ -melanocyte stimulating hormone -- and now I'm going  
8 to be a little more specific in medical treatments --  
9 many of you have heard is a very exciting peptide  
10 hormone as depicted on the right, upper-hand corner of  
11 this slide.

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

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

22 Only 1 of every 10 cells on the skin

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 rewarding experience for us.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 (Applause.)

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 We're going to try these polling questions,

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

5 Okay. Oh.

6 UNIDENTIFIED FEMALE SPEAKER: We're still  
7 waiting for ...

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

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

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

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

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

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

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

10          Okay. We have a nice mix here today.

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

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

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

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

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

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

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

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

10 MR. THOMPSON: Very similar results.

11 DR. EGGERS: Similar. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

15 DR. EGGERS: Thank you so much, Monica.  
16 Now we'll have Madelyn.

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

1 age.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15           (Applause.)

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

13 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

16 MR. MEJIAS: I might have lost it.

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

20 MR. MEJIAS: Oh, I found it.

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

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

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

6 Thank you.

7 (Applause.)

8 DR. EGGERS: Thank you, Victor.

9 And now we have Meghan.

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

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

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

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

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

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

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

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

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

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

14           DR. EGGERS: Thank you very much, Meghan.

15           (Applause.)

16           DR. EGGERS: Thank you.

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

19           MS. WILES: Just a second.

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



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

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

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

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

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

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

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

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

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

1     horrific reactions.

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

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

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

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

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

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

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

19 Thank you.

20 (Applause.)

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

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

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

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

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

1 can't even take my dogs for a walk.

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

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

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

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

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

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

11 Thank you.

12 (Applause.)

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

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

1 conversation.

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

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

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

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

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



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

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

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

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

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

22 DR. EGGERS: Okay. We heard some very vivid

1 descriptions of the burning or stinging up here by  
2 you.

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

7 And if you could state your name?

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

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

16 MS. BURTON: The burning.

17 DR. EGGERS: The burning.

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

21 DR. EGGERS: Okay. Yeah, over here.

22 UNIDENTIFIED FEMALE SPEAKER 2: I'm from

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

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

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

8 DR. EGGERS: Okay.

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

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

16 Otherwise, that person will be filming today's event.

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

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

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

4           (Laughter.)

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

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

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

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

18          UNIDENTIFIED MALE SPEAKER 2: Hello.

19          DR. EGGERS: There we go.

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

1 DR. EGGERS: Okay.

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

6 DR. EGGERS: Go ahead.

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

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

18 DR. EGGERS: Okay. Thank you.

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

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

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

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

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

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

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

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

21 MR. GARRETT: I'm David.

22 DR. EGGERS: Hi, David.

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

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

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

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

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

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

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

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

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

13 Okay. I want to ask about itching.

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

19 DR. MARCUS: Thank you.

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

22 UNIDENTIFIED FEMALE SPEAKER 3: Oh, well,

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

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

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

12 Okay. No, of course.

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

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

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

7           We have someone here.

8           UNIDENTIFIED MALE SPEAKER: (inaudible - off  
9 mic).

10          DR. EGGERS: Pardon me?

11          UNIDENTIFIED MALE SPEAKER: (inaudible - off  
12 mic).

13          (Laughter.)

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

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

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

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

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

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

18           DR. EGGERS: Thank you very much.

19           Right here.

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

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

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

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

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

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

1 after a reaction if it's bad enough.

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

5 MS. SILVEY: Leslie.

6 DR. EGGERS: Leslie.

7 MS. SILVEY: I'm Leslie Silvey.

8 DR. EGGERS: Leslie.

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

14 Depression or anxiety?

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

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

20 DR. EGGERS: Okay.

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

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

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

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

17           So just two things I definitely see that I  
18 experience.

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

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



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

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

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

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

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

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

22 How many of you would say that that fear is

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

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

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

13 DR. EGGERS: Okay.

14 UNIDENTIFIED FEMALE SPEAKER 6: And there  
15 was another lady at this table that talked about  
16 walking around with broken bones -- high fevers --  
17 103, 104 fever -- before we knew how sick she was  
18 because of her tolerance of pain.

19 DR. EGGERS: Thank you.

20 Any symptoms that you want to delve into?

21 Any more?

22 Roselyn?

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

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

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

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

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

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

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

13           Yes, Kristin?

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

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

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

4 DR. EGGERS: Thank you.

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

7 Go ahead.

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

17 DR. EGGERS: Thank you very much.

18 And here.

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

22 Before that, we knew there was something

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

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

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

22           The only good thing that came out of it was,

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

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

11 But I guess what I was kind of interested  
12 in, and maybe the show of hands, whatever, like, who -  
13 - patients in the room who've had that kind of  
14 reaction, that severe -- as a severe reaction as that  
15 --

16 DR. EGGERS: Okay. Yeah.

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

18 DR. EGGERS: I think --

19 MR. TURRELL: -- that's --

20 DR. EGGERS: Let me ask --

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

22 DR. EGGERS: Let me build on your question.

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

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

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

14 UNIDENTIFIED FEMALE SPEAKER: Spring.

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

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

19 (Crosstalk.)

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

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



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

3 KRISTIN: Sorry.

4 DR. EGGERS: Go ahead.

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

8 DR. EGGERS: That's right.

9 KRISTIN: So they don't have that reaction.  
10 (Applause.)

11 DR. EGGERS: Right. Thank you.

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

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

22 B, ability to participate or perform at work

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

7 (Crosstalk.)

8 (Laughter.)

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

14 Yeah. We're coming with the microphone.

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

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

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

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

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

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

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

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

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

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

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

14            (Applause.)

15            DR. EGGERS: Thank you very much.

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

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

1 extracurricular sports.

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

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

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

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

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

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

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

22 DR. EGGERS: Yeah.

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

10 DR. EGGERS: Okay. Thank you.

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

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

22 I can imagine if she's missing more school.

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

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

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

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

22 We definitely need to figure something out



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

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

8 (Applause.)

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

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

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

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

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

11           DR. EGGERS: Wait. I'm --

12           DR. MARCUS: Yes.

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

15           DR. MARCUS: Okay.

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

18           DR. MARCUS: Okay.

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

21           DR. MARCUS: Perfect. Okay.

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

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

4 DR. MARCUS: Okay.

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

8 DR. MARCUS: Yes, yes.

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

11 DR. MARCUS: Okay.

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

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

22 I would like to know about wind. If you go

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

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

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

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

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

22 And I think I've already gotten to the

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

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

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

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

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

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

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

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

9 DR. MARCUS: Okay.

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

12 DR. MARCUS: Yes.

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

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

20 DR. MARCUS: Right, yes.

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

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

2 DR. EGGERS: Three choices? Okay.

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

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

7 DR. EGGERS: Okay.

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

10 DR. EGGERS: Okay.

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

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

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

21 (Crosstalk.)

22 (Laughter.)

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

3 (Crosstalk.)

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

10 UNIDENTIFIED MALE SPEAKER 4: Can I say  
11 something?

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

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

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



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

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

6 MR. MOULEDOUX: Pierre Mouledoux from New  
7 Orleans.

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

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

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

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

7           DR. EGGERS: Go ahead, Kendall.

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

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

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

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

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

11 UNIDENTIFIED MALE SPEAKER 4: Thanks.

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

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

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

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

11 DR. MARCUS: Okay. Thank you.

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

16 Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

14 Dr. Teng?

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

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

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

13           DR. EGGERS: Thank you very much.

14           And Electra has a question.

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

21           DR. EGGERS: So different sensations or the  
22 same?



1 We have a comment in the back.

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

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

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

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

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

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

11          DR. EGGERS: Thank you.

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

15          SHAWN: Are you asking me, specifically?

16          DR. PAPADOPOULOS: Yes, and for everybody.

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

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

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

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

10          DR. EGGERS: Go ahead.

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

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

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

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

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

11           (Applause.)

12           DR. EGGERS: Julie?

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

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

20           (Crosstalk.)

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

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

3 (Crosstalk.)

4 UNIDENTIFIED FEMALE SPEAKER: Initially, it  
5 feels better.

6 UNIDENTIFIED FEMALE SPEAKER: Right.

7 UNIDENTIFIED MALE SPEAKER: Yeah.

8 (Crosstalk.)

9 DR. EGGERS: So short term --

10 (Crosstalk.)

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

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

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

6           DR. EGGERS: Okay. Thank you.

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

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

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

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

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

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

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

7 MS. HARVARD: Because I had --

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

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

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

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

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

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

6 I think Jonathan had a question.

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

14 (Applause.)

15 UNIDENTIFIED MALE SPEAKER: Let's hear.

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

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



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

4           (Laughter.)

5           MICHAEL: So I wear this all day, every day.  
6           It gets hot. I get heatstroke sometimes. I  
7 -- if I want to go to the mall, I wear this until I  
8 get to the mall. You can imagine how people react,  
9 right? What are you, cold? I get that every day.  
10 Are you a terrorist? People just start doing this,  
11 right?

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

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

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

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

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

15           (Laughter.)

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

18           (Laughter.)

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

1 worse.

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

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

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

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

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

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

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

11 DR. EGGERS: What's your name?

12 MICHAEL: Michael.

13 DR. EGGERS: Michael. Thank you, Michael.

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

16 (Applause.)

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

1 come back.

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

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

6 Thank you very much.

7 (Off the record.)

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

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

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

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

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

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

15 UNIDENTIFIED FEMALE SPEAKER: (inaudible -  
16 off mic).

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

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

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

3 (Crosstalk.)

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

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

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

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

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

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

1 protective clothing with an SPF. Okay.

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

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

12 How many as part of a clinical trial? Okay.

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

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

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



1 UNIDENTIFIED FEMALE SPEAKER: (inaudible -  
2 off mic).

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

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

11 DR. EGGERS: Okay. Thank you.

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

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

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

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

4 DR. EGGERS: Okay.

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

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

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

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

1 effects. Okay.

2 Any of the other treatments?

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

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

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

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

21 DR. EGGERS: Okay. Thank you.

22 Up here in the front.

1 (Applause.)

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

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

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

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

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

5 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

15 DR. EGGERS: Thank you.

16 So any final comments on alfamelanotide?  
17 Okay.

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

22 DR. EGGERS: You can say -- Scenesse is

1 easier to say.

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

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

10           (Laughter.)

11           (Applause.)

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

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

19           (Applause.)

20           DR. EGGERS: Okay. One final comment.

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



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

5           And I just have to say the -- speaking about  
6 what I'm looking for in a treatment, what Scenesse has  
7 done for me beyond my wildest dreams is just increased  
8 the amount of time I can spend outside before  
9 experiencing a reaction, that I'm trying to relearn,  
10 20, 25 years of learned behavior of hiding from the  
11 sun.

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

22           And FML -- Scenesse, just going to keep it

1 easy, has really just so surpassed my wildest  
2 expectations.

3 (Applause.)

4 DR. EGGERS: We do one more.

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

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

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

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

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

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

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

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

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

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

1 before I would start to experience some sort of  
2 reaction.

3 Now I start looking at my watch, and I see  
4 40 minutes, 60 minutes go past. And you need to fight  
5 yourself to really get over the learned behavior of,  
6 no, I've been outside way too long. And so I'm really  
7 trying to push that.

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

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

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

1 so, see how far I can push myself with these days.

2 And I'm hopeful to get up into several hours outside.

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

5 MS. LINDSTROM: Thank you.

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

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

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

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

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

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

1 actually, on the beach down in Texas.

2 I went out there, and I'm going to do this.

3 I was doing this. I'm 46, so I figured my life's half

4 over. But I think about these children that are not

5 over. And I think about what I went through, and I

6 think about they need a chance. So I'm going to do

7 what it takes for them to not suffer.

8 So I did this. And you know, I was

9 terrified. But I remember counting the steps from

10 Hotel Galvez to the beach and making sure that there

11 was a runway and telling my husband here's my purse.

12 Here's my shoes, just in case, you know, we got to

13 run.

14 But from 10 minutes to 15 minutes to 20

15 minutes and, you know, by an hour I'm thinking we are

16 really pushing this. But it is more of a we are

17 definitely scared ourselves. But I think that it's

18 just us after all these years being just taught to

19 shadow jump. And the fear of going out into light is

20 just -- we are living in darkness all of our life.

21 But that's how we had to survive.

22 These children don't have to survive like

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

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

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

15 DR. EGGERS: And what was your name again?

16 MS. IJAMES: Diana Ijames.

17 DR. EGGERS: Diana, thank you.

18 (Applause.)

19 DR. EGGERS: So --

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

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

3 MS. IJAMES: Never.

4 DR. MARCUS: Okay.

5 MS. IJAMES: I am a five minutes max.

6 DR. MARCUS: Five minutes max?

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

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

17 (Laughter.)

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



1 it's just a real intensity.

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

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

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

15 DR. MARCUS: -- less --

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

22 DR. MARCUS: So you were able to take him

1 outside?

2 MS. IJAMES: Play ball.

3 DR. MARCUS: And you played ball. Okay.

4 MS. IJAMES: We went fishing. Yay. And we  
5 got to go camping. That was exciting -- not really.

6 But there was all kinds of things that I got to do  
7 with my son that I would never have been able and I  
8 still can't do it right now until it's nighttime.

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

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

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

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

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

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

11 DR. EGGERS: Thank you very much, Diana.

12 (Applause.)

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

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

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

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

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

11           (Applause.)

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

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

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

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

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

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

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

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

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

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

7 DR. EGGERS: Thanks.

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

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

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

1 DR. EGGERS: Thank you.

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

8 And now I cover all aspects of photo-  
9 dermatology, which is a subarea in dermatology, to  
10 look at the beneficial as well as the side effects of  
11 sunlight, including photo protection, including of  
12 course the porphyrias. And I was sent as also a  
13 participant in the trial of the alfa-melanotide that  
14 was published.

15 DR. EGGERS: Thank you.

16 DR. TENG: Joyce Teng. I'm a double board-  
17 certified in dermatology and pediatric dermatology.  
18 My special interest is genetic skin diseases and drug  
19 repurposing, and I have no other financial  
20 disclosures. I did not participate in this particular  
21 clinical trial.

22 DR. EGGERS: Great. Thank you.

1           We're now going to have two presentations to  
2 level-set on the drug development and FDA's regulatory  
3 process.

4           So I'll ask Paul to come up.

5           UNIDENTIFIED FEMALE SPEAKER 15: Is Dr. Poh  
6 supposed --

7           DR. EGGERS: Excuse me?

8           UNIDENTIFIED FEMALE SPEAKER 15: She's on  
9 the panel. She just wasn't --

10          (Crosstalk.)

11          DR. EGGERS: Is she here?

12          UNIDENTIFIED MALE SPEAKER 8: She is here.

13          UNIDENTIFIED FEMALE SPEAKER 15: -- on a  
14 panel but confused about --

15          DR. EGGERS: Is she here? Is she here to --  
16 okay.

17          Then come on up. Yep.

18          And Dr. Poh, if you could introduce  
19 yourself, please.

20          DR. POH-FITZPATRICK: Good afternoon. I'm  
21 Maureen Poh-Fitzpatrick, and I'm at Columbia  
22 University in New York City. And I have been a



1 researcher on protoporphyria since the 1970s. I was  
2 principal investigator of a NIH-funded research  
3 laboratory, and we looked at basic and clinical  
4 research in EPP.

5 I've seen many patients over my career, and  
6 I think I have some insight into what may be going on,  
7 so I'm very happy to participate in any way I can  
8 today.

9 MR. PHILLIPS: Great. Thank you.

10 So as mentioned, my name is Paul Phillips.  
11 I'm a project manager in the Division of Dermatology  
12 and Dental Products here at the FDA. And this  
13 afternoon, I'm going to give you a very brief overview  
14 of the drug development and regulatory process and the  
15 different roles that are played within that.

16 During my overview, I will discuss the  
17 stages of development, beginning with discovery and  
18 moving all the way through the post-approval stage.  
19 Listed here, you'll see a few definitions that will  
20 come up today. And I will use a few of these acronyms  
21 as well as the definitions themselves. Hopefully, it  
22 will help you understand what I'm referring to as I

1 use them.

2 A point I'd like to reiterate that was  
3 mentioned earlier by Dr. Marcus and when she touched  
4 on it in her opening comments was that the drug  
5 development process is really initiated and carried  
6 out by companies, physicians, and other entities that  
7 are independent of the FDA. The FDA's role really is  
8 just to simply regulate the process to ensure the  
9 protection of the public health. So ...

10 The drug development process begins with  
11 discovery. This particular step is not one that the  
12 FDA regulates, but the next step, the non-clinical  
13 step, which is carried out in the laboratories, is  
14 where FDA begins their regulation.

15 We provide good laboratory practice  
16 guidelines for sponsors to follow. And the purpose of  
17 this step really is for sponsors to gather information  
18 sufficient to support the submission of an  
19 investigational new drug application, which as you  
20 noticed on the previous slide, allows an  
21 investigational product to be given to humans.

22 One of the purposes -- excuse me. So with

1 that, let's take a closer look at what specific  
2 information is required in order to submit an IND that  
3 the FDA could then allow an investigational product to  
4 be given to humans.

5           Listed here, the first two bullet points  
6 you'll see are both what we call product quality as  
7 well as pharmacology and toxicology information that  
8 sponsors will gather in order to support the safety of  
9 a product and be given to humans.

10           If a product has already been given to  
11 humans in either another country or in previous  
12 trials, then we also like to see the experience that  
13 was previously seen in humans with that product to  
14 help us make our decisions.

15           So once the FDA receives a new IND, the  
16 sponsor must wait 30 days before they can initiate  
17 studies of the proposed clinical trial. During this  
18 time, the FDA reviews the information in the IND to  
19 determine if the study in humans is safe to proceed.

20           At the end of those 30 days, if we haven't  
21 discovered any potential safety concerns that we think  
22 would, you know, be of harm to the subjects, then the

1 study is allowed to proceed at the end of those 30  
2 days.

3 First in -- human studies typically begin in  
4 Phase I of clinical development. I'll talk a little  
5 bit more about what that means. So Phase I of  
6 clinical development is, again, first in human studies  
7 generally. It's typically done in healthy volunteers,  
8 although there are exceptions. We heard one of those  
9 here a few minutes ago.

10 The starting dose of the drug is low  
11 compared to the dose that would be expected to produce  
12 efficacy or adverse events. And the purpose of this  
13 phase really is just to assess the safety in humans,  
14 to gather PK data and other information, such as the  
15 effect that food may have when using the drug. These  
16 studies, as well as all clinical trials, should be  
17 conducted according to good clinical practice  
18 guidelines, which are endorsed by the FDA.

19 After completion of Phase I studies, the  
20 next stage is Phase II of clinical development. New  
21 INDs for drugs which have been previously given to  
22 humans will often start in this phase. During this

1 phase, there's also a continued opportunity for  
2 sponsors to interact and receive feedback from the FDA  
3 on their development program.

4           Specifically in Phase II, these studies are  
5 typically done in volunteers with the disease of  
6 interest as opposed to health volunteers that we  
7 talked about in Phase I. These studies are usually  
8 dose ranging to determine the optimal dose for  
9 treatment.

10           Sponsors look for trends of evidence or  
11 efficacy of the drug against the disease. Sponsors  
12 also continue to assess the safety in humans, gather  
13 PK data and other information, such as the food  
14 effects that we mentioned previously.

15           One of the opportunities during this phase  
16 that sponsors have to interact with the FDA occurs at  
17 the end of this phase when sponsors can come and meet  
18 with us with what's called an End-of-Phase II Meeting  
19 where the Phase II study results and the sponsor's  
20 plan for confirmatory Phase III clinical trials can be  
21 discussed. And the FDA provides feedback on the  
22 sponsor's proposed plans in order that those studies

1 can be designed in a way to gather the appropriate  
2 safety and efficacy data that will eventually be  
3 needed for marketing application.

4 The next and typically last phase of  
5 clinical development is what we call Phase III. Again  
6 in this stage, there's additional opportunities for  
7 interaction and feedback with the FDA. Phase III  
8 trials are conducted in volunteers again with the  
9 disease of interest.

10 Now what's important is that the drug that's  
11 given has to be what we call the to-be-marketed  
12 formulation, and the dose that the drug will --  
13 basically, the product has to look like what it's  
14 going to look like when it's in -- with what the  
15 company intends for it to look like when it's going to  
16 be marketed.

17 The purpose of this stage is to generate  
18 what we call substantial evidence that the drug  
19 product is effective for the intended use. This  
20 standard of substantial evidence is set by the Food,  
21 Drug, and Cosmetic Act and is defined in the Code of  
22 Federal Regulations as being generated from "adequate

1 and well-controlled trials."

2           So generally, to the FDA this -- we  
3 interpret this to mean that we generally recommend  
4 that sponsors conduct two adequate and well-controlled  
5 trials in order to confirm the product is effective  
6 for the intended use. These trials also add to the  
7 growing safety database that we've been gathering over  
8 this period of time.

9           Again, in this stage, another opportunity  
10 for feedback with FDA occurs at the end when sponsors  
11 have the option to meet with the FDA to discuss the  
12 content and format of their eventual marketing  
13 application so that when it comes in, it's complete  
14 and in a condition that we can review it.

15           So once an applicant has then generated all  
16 of this data and gathered everything that is needed,  
17 they can submit what's called a new drug application  
18 or a biologics license application -- that's the  
19 specific term I've been referring to as marketing  
20 application -- for review by the FDA.

21           One point to note -- the FDA does not  
22 solicit these. These are submitted at the choice of

1 applicants whenever they feel that they have  
2 sufficient information to submit one of these  
3 applications. So they may do that at any time.

4 The FDA review of a marketing application  
5 actually has quite a few steps. And generally, it  
6 lasts anywhere from 6 to 12 months, depending upon the  
7 type of application that is submitted.

8 The marketing application review process --  
9 I'm going to go into a little bit more detail because  
10 I think this is one that's important. The first step  
11 that FDA takes after we review an NDA or a BLA is to  
12 determine whether or not the application is complete.

13 In other words, does it contain all the data  
14 elements that are outlined by the Code of Federal  
15 Regulations? Applications for a drug that contain an  
16 active ingredient never marketed before in the U.S.  
17 typically allow an extra two months for FDA to make  
18 that determination of completeness.

19 If an application is complete, it's filed,  
20 and the scientific review then begins. During the  
21 review of the products -- of products with a new,  
22 active ingredient, FDA will often hold a public



1 advisory committee meeting to gather outside expert  
2 input.

3           There are discussions about the product  
4 labeling that occur between the FDA and the applicant  
5 during the review process. Substantial evidence is  
6 determined by FDA's scientific review of the data  
7 submitted in the application. This determination,  
8 along with other recommendations from the review team,  
9 contribute to an overall benefit risk decision, which  
10 was mentioned earlier, again, by Dr. Marcus.

11           And that means just the decision about  
12 whether the benefits of the drug to the intended  
13 patient population are likely to outweigh the known or  
14 potential risks of the drug to the intended  
15 population.

16           Based on that benefit risk assessment, a  
17 final decision is made by the FDA to either approve  
18 the drug product for marketing in the United States or  
19 to issue a complete response, which is a non-approval  
20 that contains deficiencies for the applicant to  
21 resolve before the drug can be approved.

22           For drug products which are approved, the

1 development of the product then continues in what we  
2 call the post-approval or post-marketing stage. In  
3 the post-approval stage, FDA continues to monitor the  
4 safety information of the drug product from a variety  
5 of sources, including adverse event reports, which we  
6 receive in our new FDA Sentinel system, which has  
7 recently been stood up.

8 Sponsors continue to develop their product  
9 in a variety of ways. I'll mention two. One is an  
10 example of them addressing the Pediatric Research and  
11 Equity Act, or PREA, to study the drug in children to  
12 generate information for labeling that will guide  
13 prescribers who treat children with the disease of  
14 interest.

15 These required pediatric studies are often  
16 not done, although there are exceptions to this. But  
17 these are generally not done until after sufficient  
18 safety information is gathered in adults. Therefore,  
19 because of that, a drug is often first approved in  
20 adults, and then the pediatric development occurs  
21 post-approval in children.

22 Another example of the development and post-

1 approval stage is when a sponsor chooses to  
2 investigate the use of their product to treat other  
3 diseases than that which it was initially approved  
4 for. In that case, sponsors usually start back again  
5 at Phase II of development and work their way  
6 iteratively through the process we just described  
7 until they have sufficient safety and efficacy data to  
8 submit to the FDA for review of a new indication.

9 This iterative process of additionally  
10 gathering safety and efficacy data throughout the  
11 lifecycle of a drug, in particular in the post-  
12 approval stages, continues until a company comes to a  
13 point where, for a variety of reasons, whether for  
14 safety or business decisions or other reasons, they  
15 may choose to stop marketing the product and  
16 manufacturing their product.

17 And that typically marks the end of the drug  
18 life cycle in the development process as we think of  
19 it as a whole.

20 So with that, that concludes my remarks, and  
21 we'll turn the time now to Dr. Kathryn O'Connell.

22 DR. O'CONNELL: Good afternoon. My name is

1 Kathryn O'Connell, and I'm a medical officer in the  
2 Rare Diseases Program, which is a program within the  
3 Center for Drug Evaluation and Research.

4 And before I say a few words, I would like  
5 to thank you all very much for coming here today and  
6 helping us learn about this disease. It's very  
7 important to us, and we appreciate it.

8 We're a little short on time today, so  
9 basically I'm just going to build on what Paul has  
10 already talked about by talking a little bit about the  
11 approval process in the context of rare diseases. And  
12 Jonathan and I are both on the panel this afternoon.  
13 So if there's anything that's of particular about this  
14 topic or other rare disease topics, we can maybe work  
15 on it then.

16 So the first thing that I wanted to -- like  
17 we said this morning, get everybody on the same page -  
18 - is what are we talking about when we talk about a  
19 rare or an orphan disease? So a rare disease is  
20 defined in the Orphan Drug Act -- and many of you  
21 probably already know this -- as a disease or  
22 condition that affects less than 200,000 people in the

1 United States. That's generally what it means.

2 And so an orphan drug is a drug or a  
3 biological product that's used for the prevention,  
4 diagnosis or treatment of a rare disease in the United  
5 States. So with that in mind, we can look at actually  
6 what the Orphan Drug Act did.

7 So that was in 1983, and the Orphan Drug Act  
8 actually was enacted specifically to stimulate product  
9 development for rare disease conditions, as we just  
10 defined it, for the diagnosis, prevention or treatment  
11 among other things. There are other things the Orphan  
12 Drug Act does.

13 But among the major things that it does are  
14 financial incentives that were -- that are designed to  
15 encourage sponsors to study -- you know, to study and  
16 develop drugs.

17 So this is the reason I brought those points  
18 up because this is a really important point. The  
19 Orphan Drug Act did not alter the statutory standard  
20 for drug approval. And so what that means is that  
21 regulatory requirements and the process for obtaining  
22 marketing approval in the United States are the same

1 for drugs granted orphan designation through the  
2 Orphan Drug Act as for common disease drugs.

3 And this surprises people. And sometimes  
4 I've even heard people say, oh, that must have been an  
5 oversight, you know, when they made the Orphan Drug  
6 Act, but it isn't. It was not an oversight -- I'm  
7 going to talk about why -- because the real principle  
8 here is that people affected by rare diseases deserve  
9 the same level of drug quality, safety, and efficacy.

10 So you're asking yourself, like most people  
11 do, well, how can the same standards apply to a  
12 disease where there may be only 35 people compared to  
13 diseases where there's millions of people.

14 And the fact is that special standards for  
15 orphan drugs are unnecessary because the regulations  
16 that FDA works under already had in place specific  
17 language about flexibility and judgment on the part of  
18 the FDA in applying those standards.

19 And it doesn't specifically call out rare  
20 diseases. But it calls out the special circumstances  
21 and conditions of diseases, and then flexibility is  
22 applied as needed. And so, you know, in fact, many

1 rare diseases that are approved, flexibility was and  
2 is applied during the decision-making process.

3 So what are the approval essentials? So in  
4 the United States, what is the bottom line? What do  
5 you need? So the first thing is you need substantial  
6 evidence of effectiveness for treatment of the  
7 proposed indications. So the indication is, you know,  
8 the disease.

9 The second thing you need is a demonstration  
10 that the benefits of the drug outweigh the risk for  
11 the patient population for which the drug is  
12 indicated. And then the third thing is that there has  
13 to be a manufacturing process in place that ensures  
14 what the drug is in the marketplace and the strength  
15 of it, the quality, et cetera.

16 And then the fourth thing is that there  
17 needs to be, you know, evidence-based drug labeling.  
18 So labeling isn't the thing on the bottle, but it's  
19 the prescription, the sheet of information that the  
20 doctors get, that you get, that adequately guides  
21 prescribers and patients so that the drug can be used  
22 safely and effectively, essentially describes what is

1 known about the drug.

2           So again, this is such an important point.

3 I just want to mention a couple things about it. So  
4 the regulatory requirement for approval in the United  
5 States, as Paul mentioned already, is demonstration of  
6 substantial evidence of effectiveness. And that  
7 generally requires studies designed well enough to  
8 distinguish the effect of a drug from other  
9 influences, such as a spontaneous change that would  
10 have happened even if, you know, the patient hadn't  
11 been exposed to the drug.

12           And examples of spontaneous change would be  
13 a placebo effect or a biased observation. And biased  
14 in this case doesn't have the context that it does in  
15 the outside world. It just means that it's an  
16 observation that isn't -- it -- where there could be  
17 things that affected the observation that weren't  
18 planned.

19           So basically, that's the requirement. And  
20 then as I already said, the benefits need to exceed  
21 the risks under the conditions stated in the labeling.  
22 And as Paul mentioned, the usual approval standard is



1 two adequate and well-controlled studies.

2           However, as I noted before, FDA has applied  
3 the flexibility that I talked about, very often to  
4 rare disease drug review and approval. And in fact,  
5 in 1997, the FDA Modernization Act, you know,  
6 specifically stated and clarified that FDA can  
7 consider data from one adequate and well-controlled  
8 clinical investigation with confirmatory evidence to  
9 constitute substantial evidence.

10           If you want to know more about this, this is  
11 the name of the guidance that you can refer to. You  
12 can get it on -- you know, on the Internet. And it  
13 talks about the scientific reasons why FDA doesn't  
14 generally rely on a single study.

15           And it's usually reserved for situations  
16 where there's a clinically meaningful effect on  
17 mortality, irreversible morbidity or prevention of a  
18 serious disease and situations where it really is not  
19 feasible to do a confirmatory trial. So basically,  
20 it's a judgment call, as we talked about a few minutes  
21 ago.

22           And the last thing I'm going to just say

1 here -- and then I'm going to stop so that we can get  
2 sort of back on schedule here -- is the safety piece  
3 of this. So the safety evidence for approval to  
4 support, you know, a marketing approval, is also a  
5 judgment call.

6 And it's based on the overall assessment of  
7 the risk and the benefit within the context of the  
8 disease. So again, you need, you know, a  
9 demonstration of substantial evidence of effectiveness  
10 so that you got that part of the equation. And then  
11 the benefits of that drug must exceed the risk under  
12 the conditions stated in the labeling.

13 So I think I'll stop there. And like I  
14 said, we're on the panel. And during the panel  
15 discussion, if you want to bring any of this up,  
16 please do.

17 Thank you.

18 (Applause.)

19 DR. MINDER: Ms. Marcus, dear friends and  
20 colleagues, I thank you very much for me to present  
21 challenges in clinical trial design in EPP.

22 Here you can see my conflict of interest

1 statement. Actually, I never had a personal benefit  
2 from cooperation with pharma companies. My motivation  
3 is the wellbeing of my patients.

4 Our exercise in porphyria covers more than  
5 45 years. We care for 500 Swiss and many patients --  
6 many porphyria patients from other countries. Since  
7 1990, our focus is on EPP, and we have cared for more  
8 than 100 patients.

9 Our analysis of beta-carotene trials  
10 illustrates the necessity of high-quality trials.  
11 Low-quality trials result in falsely high efficacy.  
12 The recently published cimetidine trial would nicely  
13 fit in this diagram and would localize here.

14 So first challenge in trial design is to  
15 define EPP. It is simple for porphyria experts --  
16 phototoxic episodes since infancy or early childhood  
17 and significantly increase protoporphyrin. Symptoms  
18 and burns (ph) in a designated period gets described  
19 for Phase III for the cimetidine trial is  
20 characteristic of congenital erythropoietic  
21 protoporphyrin, which is a different disease.

22 The second challenge is to find the

1 rationale for treatment. Skin barriers to prevent  
2 photo activation of protoporphyrin, scavenging of  
3 oxygen radicals or other inflammatory compounds  
4 generated by light activated protoporphyrin,  
5 mitigation of local skin inflammation and improvement  
6 of survival and inhibition of ALA-synthase 2 are  
7 rationales used until now.

8 In the last decades, our team applied  
9 without success all compounds with stars on this  
10 slide. Thus, we gained a broad experience with  
11 ineffective treatments in EPP, including self-tanning,  
12 sunscreens, beta-carotene, cysteine, antihistamines.

13 With carefully dosed UVB treatment, we found  
14 a slight -- a really slight improvement in some  
15 patients. However, most of them did not tolerate it  
16 because it was too painful for them. The only drug  
17 that was highly effective was alfa-melanotide.

18 We did not use cimetidine because its  
19 preclinical evidence is insufficient, as shown on the  
20 next slide. Every publication on cimetidine in any  
21 kind of porphyria refers to the 1984 publication of  
22 Marcus (ph). He showed in whole animals a short lift

1 decrease of ALA-synthase activity for 30 minutes  
2 followed by an increase to a level higher than  
3 initially.

4           Thus, second, cimetidine did not inhibit  
5 ALA-synthase activity directly. Thus, the observed  
6 decrease is due to a liver specific regulation of ALA-  
7 synthase. As in bone marrow, ALS-synthase activity is  
8 definitely regulated. An effect of cimetidine on  
9 protoporphyrin synthesis in EPP is unlikely, and I can  
10 add I just heard yesterday that John Philips and Bob  
11 Desnick have additional data on this.

12           So the challenge is similar for all rare  
13 diseases. Complexity of disease negatively affects  
14 outcomes. High variability of symptoms reduces  
15 statistical significance. Adaptation due to early  
16 onset in life leads to an overestimation of quality of  
17 life before an effective treatment.

18           Minor positive changes may be important to  
19 patients. Also, we as healthy persons may consider  
20 them as insufficient. We know these problems also  
21 from quality attested life years.

22           Last, if there is no preexisting effective

1 treatment, it is impossible to validate an outcome  
2 instrument.

3 But let's go back to EPP. EPP is not the  
4 simple sunlight sensitivity, and in EPP, irradiants  
5 does not correlate to the extent of photo damage.

6 We all agree that EPP patients are sensitive  
7 to light, to direct sunlight, to sunlight passing  
8 through windows and to sunlight reflections at the  
9 beach or in the snow. However, bright sunshine is  
10 less offending than overcast sky.

11 Many patients suffer from indirect light,  
12 both outdoors and indoors, and more and more patients  
13 complain about artificial lighting, especially the new  
14 energy saving bulbs. Wind, temperature and air  
15 humidity modifies symptoms.

16 We even do not exactly know which  
17 wavelengths are damaging. Blue, we all agree yes  
18 because it's a major absorbance found of  
19 protoporphyrin. Red, most likely because, in  
20 photodynamic therapy, it is a yet organic (ph) local  
21 EPP. It uses red light.

22 As we emphasized before, many patients react

1 to UV. Also, protoporphyrin does not absorb at these  
2 wavelengths. And we have determined that  
3 protoporphyrin has absorbance bands in the infrared.  
4 And at least during phototoxic episodes, patients are  
5 very sensitive to heat.

6 The effect of latitude is illustrative that  
7 the lack in correlation of irradians and photodamage.  
8 Also, irradians is highest in equatorial regions.  
9 EPP patients have reduced symptoms or even no symptoms  
10 in tropical areas.

11 As a young physician, I recommended the  
12 parents of my EPP children to spend their holidays in  
13 the northern countries because I thought EPP children  
14 may benefit from reduced light intensities. That was  
15 wrong. Symptoms are increased in higher latitudes.

16 Phototoxic damage does not follow certain  
17 rule that a certain intensity of an offending action  
18 determines a certain degree of damage. Well known in  
19 medical literature and also cited today is the priming  
20 phenomenon.

21 If a patient is light-exposed one day, he or  
22 she is more sensitive to light the next day, but it is

1 even more complicated. Patients speak of a light  
2 account for four, five or six days. They can expose  
3 to light, but when their light account is empty, they  
4 get really sensitive to light and easily burned.

5 So extraordinary disease variability is  
6 illustrated by the 14 times variation of its  
7 biomarker, protoporphyrin, in the Swiss cohort. The  
8 same is true for United Kingdom patients, if you just  
9 look at the X values of the lower graph.

10 This graph also makes a correlation between  
11 protoporphyrin concentration and quality of life, as  
12 measured by the dermatological quality of life index.  
13 The authors found a positive correlation. However,  
14 higher life quality with higher protoporphyrin levels  
15 is clinically nonsense and this qualifies the TLQUI  
16 for measurement of quality of life of therapeutic  
17 effects in EPP.

18 This leads us to the first challenge, the  
19 endpoints. Sunlight exposure and pain intensity are  
20 possible but complementary endpoints. Why  
21 complementary?

22 On therapy, one patient may tolerate a



1 certain pain level and expose longer to the light.  
2 Another one may not need to expose longer to the light  
3 but he happy if he has less pain. If only one or the  
4 other is measured, outcome measurement loses  
5 sensitivity.

6 The only biomarker I can think of in EPP is  
7 protoporphyrin. Its value is limited in a treatment  
8 intending to its reduction. That is cimetidine.  
9 Quality of life is an important outcome in EPP. TLQUI  
10 and SF36 do not qualify. EPP specific quality of life  
11 questionnaires has high discriminatory power.

12 As you see, the black or the untreated  
13 patient and the open scales are the treated patients  
14 by alfamelanotide. There's also a sensitive method as  
15 seasonal effects by a slight decrease during summer  
16 months is observed during alfamelanotide treatment,  
17 which is a clinically reasonable finding.

18 Let's go back to the complementary  
19 endpoints, sunlight exposure and pain intensity. The  
20 X-axis of this graph displays 15 minutes block, and  
21 the Y-axis pain intensity.

22 We asked the patients imagine you get a new

1 treatment against EPP symptoms, and at a sunny, summer  
2 day during lunchtime, you're outside in the sun for a  
3 certain time, which results in a certain pain  
4 intensity. Estimate the effectiveness of this new  
5 treatment.

6           You can see that the patient rated  
7 effectiveness to be 0 if they suffer from a pain  
8 intensity 10 after one quarter of an hour of sun  
9 exposure. That's meaningful. But look at that.  
10 Patients estimated the effectiveness to be 70 percent  
11 if they do not have pain after only 15 minutes sun  
12 exposure, and it goes up to 90 percent after half an  
13 hour of sun exposure without pain.

14           What I said before, minor effects, what we  
15 as healthy would question to be a substantial benefit  
16 are important to patients. Interestingly, Longendock  
17 (ph) and coworkers used exactly this outcome -- sun  
18 exposure without pain in the Phase III trial on  
19 alfamelanotide.

20           Their results on 89 U.S. and 74 European  
21 patients demonstrated a significant benefit of  
22 alfamelanotide. This endpoint is not the surrogate

1 marker. It's a direct measurement of the limitation  
2 caused by EPP, and the number of patients in a disease  
3 of the rarity of EPP is impressive. These trials as  
4 such will fill high-quality standards.

5 Certainly, pigmentation or skin coloring may  
6 induce a bias in a double-blind trial. Corbit (ph)  
7 found no effect of beta-carotene versus placebo.  
8 Also, he noted unblinding of spasi (ph) active  
9 compound. His outcome was measured by -- measurement  
10 were diaries. Such diaries are robust against  
11 unblinding. In contrast, Norris (ph) emphasized a  
12 rather strong placebo effect using retrospective  
13 questionnaires.

14 The last challenge is to convert statistical  
15 and clinical efficacy. Clinical efficacy, in my mind,  
16 is not a scientific term. It's common sense of  
17 healthy persons. Patient's attitude may be different.  
18 If no validated comparator exists, statistical  
19 significance should be considered as clinical  
20 efficacy, in my opinion, especially in a rare disease.

21 Averaging sun exposure per day results in  
22 misleading values as rainy days, staying inside due to

1 work, habit. And also, we have heard lifelong  
2 conditioning dilutes the effect. In EPP --

3 (Applause.)

4 DR. MINDER: In EPP, the contribution of  
5 patients to validate clinical efficacy is crucial.

6 They informed us on a recurrent --  
7 recurrently on ineffective treatments, as we have  
8 heard before. With respect to alfaelanotide, patient  
9 considers this drug as lifechanging. They sacrifice a  
10 lot of personal money and time to get it, and they  
11 adhere to long-term treatment under routine conditions  
12 -- in our eyes, a compelling evidence of efficacy.

13 I thank you for your interest.

14 (Applause.)

15 DR. EGGERS: All right. Thank you for three  
16 very informative presentations.

17 We are now going to move into a facilitated  
18 discussion with the panel members. I think we'll have  
19 about an hour or slightly less. I will try to squeeze  
20 as much as we can out of this as well.

21 I'm going to stand here because, well,  
22 frankly, I need to lean on something.

1 (Laughter.)

2 DR. EGGERS: So I will be standing here.

3 The discussion topics, broadly speaking,  
4 will follow the themes that -- many themes that were  
5 outlined by Dr. Minder's presentation, other things  
6 identified by FDA as being important to talk about,  
7 considerations when defining the EPP trial population,  
8 choosing the appropriate endpoints that can be  
9 reliably measured and interpreted and that demonstrate  
10 a clinically meaningful benefit, what types of  
11 measures, other clinical trial design considerations,  
12 and then some on patient and caregiver experiences in  
13 clinical trials.

14 Now, this is more than we can cover in an  
15 hour, so I will ask my colleagues at FDA to guide  
16 where you think is important. And we also have a  
17 polling question to elicit from the experts in a few  
18 minutes what you think are important considerations  
19 for trial design as well.

20 But first we want to -- we have a couple  
21 polling questions for those of you in the audience,  
22 the patients and caregivers on behalf of a patient as

1 well as on the web. We're thinking about clinical  
2 trials now, so we're moving into thinking about your  
3 participation in a clinical trial.

4 And the first one is have you or your loved  
5 one ever participated in any type of clinical trial  
6 studying an experimental treatment for EPP? So A for  
7 yes and B for no.

8 Okay. So this is so deceiving. Don't look  
9 at the size of those bars. It is about 50/50. Half  
10 of you in here have participated in a clinical trial,  
11 so we have a wealth of experience here in the room.

12 And on the web?

13 MR. THOMPSON: About 40 percent for yes and  
14 about 60 percent for now.

15 DR. EGGERS: Okay. Thank you for  
16 participating in clinical trials. It is vital to the  
17 development of safe and effective drugs.

18 We'll move on. So if you or your loved one  
19 had the opportunity to participate in a clinical  
20 trial, in a future clinical trial, to study an  
21 experimental treatment, would you consider  
22 participating? A, if yes, it would depend on many

1 factors, but I'm generally willing to consider  
2 participating. B, no, I would probably not consider  
3 participating. Or C, maybe, I'm not sure if I would  
4 generally be willing to participate or not.

5 Okay. So three-quarters of you in the room  
6 today would generally -- that you are willing to  
7 consider participating with some of you saying no and  
8 about a fifth with maybe.

9 Okay. We're going to have one more polling  
10 question to get into some factors you might take into  
11 account. And I can already tell you we haven't gotten  
12 the right factors. There are many, many factors.

13 Can we go to the next slide?

14 By the way, we only get to go to I on here,  
15 so we only get nine things to put up on our polling.  
16 And these were the factors that we thought might be a  
17 place to start when thinking -- that you might be  
18 thinking about if you were deciding -- the biggest  
19 factors you would take into account if you had the  
20 opportunity to consider participating in a clinical  
21 trial for an experimental EPP treatment.

22 So we'd like you to think through these and

1 choose up to three factors that would weigh most into  
2 your decision-making if you were considering  
3 participation. A, the complexity of the study  
4 requirements, what you have to do on treatments --

5 UNIDENTIFIED FEMALE SPEAKER 12: Any trial?

6 DR. EGGERS: For a trial. For any trial for  
7 experimental EPP treatment. Okay.

8 UNIDENTIFIED FEMALE SPEAKER 12: Not trials  
9 we've already done. You want to us --

10 DR. EGGERS: No. A new trial has come.  
11 Imagine a new trial. You are thinking about whether  
12 you would like to participate. What are you taking  
13 into account? The complexity of the study  
14 requirements, the things you have to do.

15 B, the eligibility criteria, such as the  
16 exclusion requirements. C, the location of the study  
17 site. D, concerns about side effects. E, the  
18 possibility of a placebo as a control. F, the need to  
19 stop any current medications. G, the trial duration,  
20 so how long that trial is going. H, concerns about  
21 informed consent procedures. Or I, other.

22 And H would be informed consent procedures



1 for you or your child. Any of these would be the  
2 considerations for your child if that -- if your child  
3 is the one participating.

4 Okay. So a wide range of thoughts and  
5 perspectives out here with half of you saying the  
6 location of the study site. And then about four-  
7 tenths of you in here are saying concerns about side  
8 effects and the complexity of the study requirements.

9 Okay. So we will be coming back to you to -  
10 - maybe through show of hands or for a few comments as  
11 we continue going through the rest of the panel  
12 discussion.

13 But we thought it would be important to  
14 prime this discussion by thinking what is important,  
15 what might be on study participant's mind when you  
16 think about clinical trials.

17 Okay. So with that, I'm going to segue --

18 UNIDENTIFIED FEMALE SPEAKER 12: I'd like  
19 to hear what Dr. Phillips's evidence is.

20 DR. EGGERS: You know, there --

21 UNIDENTIFIED FEMALE SPEAKER 12: Is that  
22 possible?

1 DR. EGGERS: I'm not sure if we're going to  
2 be able to answer the question now. The question was  
3 about evidence that was raised during one of the  
4 presentations, if you're on the web and can't hear in  
5 the room, and whether that evidence can be shared.

6 I'm not sure if we have the answer or if  
7 that's within the scope of today's discussion.  
8 However, I would encourage that to be submitted to the  
9 public docket, nonetheless.

10 And Kendall, do you --

11 UNIDENTIFIED FEMALE SPEAKER 12: I mean,  
12 here's here. I thought maybe he could --

13 DR. MARCUS: So I just want to give a little  
14 bit of direction to everybody about the purpose of  
15 this. And I just want to build on the comments that  
16 I've already provided in that I think that successful  
17 treatment is often a series of small, incremental  
18 steps.

19 And our purpose today is fairly broad  
20 reaching. I want to acknowledge that many people in  
21 the room participated in the clinical trials of  
22 alfamelanotide. I don't want to dwell on that because

1 there is other work that can be done. And as I said,  
2 why would you ever stop at a certain amount of  
3 benefit, similar to the transformation of treatment  
4 for HIV?

5 So in that vein, I would like to think  
6 broadly about clinical trials so that we can build  
7 upon the experience that we have in order that a  
8 clearly -- that we can learn from the past to have  
9 clearly defined and improved ways of measuring benefit  
10 and success.

11 And then the last piece I just want to keep  
12 in mind for everybody is that, particularly with a  
13 rare disease, I think the most difficult clinical  
14 trial to design would be one for pediatric patients.  
15 And I would like to know, you know, what children --  
16 what treatments can be offered to children and what  
17 can be made available to them.

18 And now we're talking about an extremely  
19 small population from which to draw in order to  
20 determine a safe and effective dose. And so we have  
21 to think very carefully. And this is why I am asking  
22 a lot of questions, just trying to parse out small

1 increments of benefit that can be measured  
2 successfully in a small number of patients.

3 So I hope that helps you understand the  
4 purpose of this discussion today. I don't want it to  
5 -- I just would like people to think broadly and think  
6 in a forward manner. I think -- I've heard from a  
7 number of patients today that they're here because  
8 they'd like to see the children in the room benefit  
9 from being here. And so do I.

10 And as I said, that's going to be a  
11 particular challenge, defining effective treatments  
12 for children because, obviously, you want any patient  
13 to be treated as soon as they're diagnosed.

14 So I hope that's helpful. I think I'm  
15 rambling now. So ...

16 DR. EGGERS: There's also -- I'll just put a  
17 reminder. There is a time for open public comment at  
18 the end of the day. The signup sheet is over by  
19 Meghana, if you raise your hand. We have 15 minutes  
20 set aside for open public comment.

21 Meghana, can you --

22 MS. CHALASANI: Ten.

1 DR. EGGERS: Ten? I'm sorry. We have 10  
2 minutes set aside for open public comment, and we can  
3 take up to six people.

4 So Meghana, can you stand so people can see  
5 where you are? Great.

6 Okay. And I've also been notified that the  
7 kiosk where you bought your snacks and lunch will be  
8 closing in five minutes. So if you need a last snack,  
9 please do so now. Okay.

10 With that said, as a way to guide discussion  
11 for the next 45 minutes or 50 minutes, we're going to  
12 ask the experts only a polling question.

13 Does everyone have a clicker? And it's  
14 right there in front of you. You can look on the  
15 screen there. Do all of you have a clicker? Okay.

16 Again, there are numerous challenges in  
17 designing clinical trial programs and trial designs.  
18 But of the following factors, which are the most  
19 significant do you think to address in designing a  
20 robust and feasibly clinical trial?

21 You can choose up to three factors --  
22 understanding that natural history of EPPA;

1 appropriately defining the trial population; choosing  
2 endpoints that are meaningful to patients; D, choosing  
3 endpoints that can reliably be measured and  
4 interpreted; E, choosing an appropriate control; F,  
5 selecting an appropriate trial duration; G, addressing  
6 the complexity of study protocols and requirements for  
7 the participants; H, recruiting and retaining trial  
8 participants; or I, something else.

9           Okay. Oh, we have seven. Did all the  
10 experts answer? Just the experts, please. Okay.  
11 Okay.

12           So of -- this is -- again, this is not a  
13 scientific poll. It's just to see -- get a gauge on  
14 where you might be in your thinking about what's  
15 important.

16           And choosing endpoints that are meaningful  
17 to patients was by five of you, followed by choosing  
18 endpoints that can be reliably measured and  
19 interpreted. So we will get at that balance in a  
20 little bit.

21           Okay. So the considerations when -- do we  
22 want to -- we'll start with defining the EPP trial

1 population. And the question -- we'll just go --  
2 we're going to go down the line. And when you think  
3 about defining a trial population, let's do a round  
4 robin. And briefly -- think is most important to  
5 consider when defining the trial population. And then  
6 we'll follow up that my colleagues might have  
7 something more to tie on for that.

8 But first, unless you have a clarifying  
9 question, we'll go through each of you. Very briefly,  
10 say what's the most important, if this is your area of  
11 expertise, about defining a trial population to keep  
12 in mind.

13 DR. DESNICK: Let me kick it off. I think  
14 the most important thing that you mentioned was  
15 understanding the natural history of EPP. You cannot  
16 design a trial unless you really understand that. You  
17 cannot pick the endpoints until you understand that,  
18 and everything else falls up from that.

19 And I thought Henry Lim did a very good job  
20 this morning when he quoted from the Holmes paper. In  
21 over 200 patients -- and they knew that the first  
22 thing that happened is patients get a prodrome.

1 That's an early symptom.

2           And that symptom, whether it's tingling,  
3 burning, itching -- it varies -- that's the warning  
4 signal to get out of the sun. And that -- once you're  
5 burned the very first time, the patients have an  
6 inherent inborne -- it's psychological avoidance of  
7 sun and light.

8           And all they can think about is how to stay  
9 out of the sun. And that's the whole clue to this  
10 disease because the minute they stay beyond the  
11 warning signal, they burn. And they are laid up, and  
12 they lose their time from work. They lose their time  
13 from school. They suffer tremendous pain.

14           (Applause.)

15           DR. DESNICK: I don't think that came across  
16 this morning because I don't think patients are  
17 suffering when they're not exposed to the sun. I  
18 think the patients avoid the sun so they don't have to  
19 suffer. And I think how much time -- can spend in the  
20 sun without pain.

21           Pain is the issue, and you want to avoid it.  
22 And I think that's what we really have to understand



1 first about the disease. And I think the applause  
2 that I got means that you all agree. And I think  
3 that's the key to understanding how to do the rest,  
4 how to define the endpoints.

5 The second thing is trial population. Well,  
6 the FDA tells you. You start with adults. Sometimes  
7 you can go 16, age of consent. And once you get  
8 something approved, there's -- you can go to a  
9 pediatric population.

10 Being a pediatrician, I know about ages and  
11 so forth where kids can do it. At Sinai, we've  
12 carried out a lot of clinical trials with young people  
13 or we have used approved drugs in young children. And  
14 there's probably an age, four to six, in which you can  
15 get some reliable cooperation. And after that, you  
16 know, you have to think through because individual  
17 kids are more mature, some than others.

18 And then, the endpoints to me are very  
19 clear. And I think that we can sit down and talk  
20 about what an endpoint is for an adult who can  
21 actually write a diary, who can carry out and look at  
22 the day and know what they're going to do.

1           And then again, with this disease, it  
2 becomes a huge challenge. And the challenge is to ask  
3 people to go out in the sun to get pain. It's almost  
4 unethical because --

5           (Applause.)

6           DR. DESNICK: And how can you ask placebo  
7 patients to do that?

8           So -- and then we have to think about  
9 endpoints. Well, if it's a drug or a treatment that  
10 is going to focus on the primary enzymatic defect,  
11 that's one thing. If it's going to focus on lowering  
12 the proto levels, that's another thing.

13           We don't have a treatment like that yet. I  
14 think they'll come in the future, and we'll have more  
15 targeted therapy. But at this moment, we don't have  
16 the laboratory measurements that can be made that will  
17 -- we know how to do them. But until some treatment  
18 comes along that focuses on either the substrate or  
19 replacing the defective enzyme or stimulating it, we  
20 don't have that choice.

21           And in fact, what we're doing right now is  
22 we're trying different sunscreens, beta-carotene, this

1 and that, and trying to increase pigmentation. And  
2 that's the only thing that we've seen so far that  
3 gives us any evidence of, you know, more time in the  
4 sun. And I don't say it. We were investigators, but  
5 you know it. So I think it becomes very complex.

6 And I'll just turn to one other quick thing,  
7 and that's children. It is extremely hard, as any  
8 parent can tell you, to have reliable reporting in a  
9 diary or anything like that of your child. And even  
10 you forget. And I think that there are plenty of  
11 studies that bear that out, whether you're doing diary  
12 or whatever.

13 So -- and I think that the other kind of  
14 objective, I know that one thing that we thought might  
15 be very objective in the beginning we've learned  
16 wasn't. Maybe Maureen Poh will talk about it, but  
17 that's photo-provocation where you're paining the  
18 patient to know how long it takes to burn. And it  
19 turned out just to be too variable. And Maureen  
20 studied it, and maybe she'll comment on it.

21 But I think these are the issues. And I  
22 must say I'm awed by Dr. Minder, who went through and

1 talked about all the challenges here. This is one of  
2 the toughest diseases to come up with a viable trial  
3 design and endpoints that will really prove it other  
4 than quality of life and time in the sun. I just  
5 don't know any others. And to me, those are ones that  
6 we've learned over a dozen years of working with one  
7 particular drug.

8 Now, when more targeted therapies come that  
9 aren't just increasing pigmentation, although that's a  
10 novel way of doing it, then maybe we can measure proto  
11 -- maybe we can measure efficacy (ph), et cetera.

12 DR. EGGERS: So there's a lot to unpack in  
13 there. So let's work on the thing that the most of  
14 you did, and let's follow up and build on what Dr.  
15 Desnick said, the balance between choosing endpoints  
16 that are meaningful to patients -- the balance and the  
17 challenges with choosing endpoints that can be  
18 reliably measured and interpreted.

19 Anyone else on the panel want to build on  
20 those comments?

21 Go ahead, and then we'll go to Manisha.

22 DR. MINDER: Okay. I said my opinion, and

1 confirmed with what Bob Desnick said. That is we have  
2 a decade of experience to measure efficacy in EPP.  
3 And I think we just come to the same conclusion as Bob  
4 Desnick did.

5 DR. EGGERS: Okay. Would you like to ...

6 DR. BALWANI: I have to agree with Dr.  
7 Minder and Dr. Desnick. You know, we've been working  
8 with clinical trials in this patient population for a  
9 while, and we've thought about this extensively.

10 And we've all come to the same conclusion,  
11 that we need a patient-reported outcome, and it's  
12 pain-free sun exposure. Improvement in quality of  
13 life is also an additional outcome, but I think we  
14 need to hear what the patients want and that is the  
15 ability to spend more time in the sun so they could  
16 have a more normal life.

17 DR. EGGERS: Okay.

18 MR. LEE: I agree with what has been said.  
19 I think for the provocation, I'm sure Maureen will  
20 talk more. It has been -- at least in photobiology  
21 world, has been very agreeable for any type of  
22 porphyria patients. This -- the results have not been

1 very consistent.

2           With other forms of photosensitivity, we can  
3 use UV to measure the redness on the skin. But with  
4 porphyria you're looking for pain, and it's very, very  
5 unreliable in terms of -- very inconsistent in terms  
6 of the result. So I think patient-reported outcome is  
7 still the best measure for this.

8           DR. EGGERS: Okay. Go ahead.

9           DR. TENG: I agree with everyone said. And  
10 I think -- honestly, I'm actually having trouble to  
11 pick out A, B, C, D, E because there -- well, A, B, C,  
12 D, and they're so interrelated.

13           Just like Dr. Desnick talked about, if we  
14 don't know the natural history of this disease and  
15 understand the intermittent nature and the episodic  
16 nature of this disease in this condition and the pain  
17 and taking the quality of the discomfort that you all  
18 experience, whether it's burning, itching and pain,  
19 they all vary. And it's going to be very difficult to  
20 define these clinical endpoint. So getting a really  
21 good natural history is very, very important.

22           The only thing that I want to add on to the

1 panel discussion is about defining the disease  
2 population and stratify the patient population.

3           And you know, we think about a lot of the  
4 genetic disease that over the years there's so many  
5 expert here can talk about the disease and the  
6 mechanism itself, with the new technology, again, that  
7 we develop a new understanding about the molecular  
8 biology of the disease and perhaps that, you know,  
9 it's time to rethink of the disease, to try to  
10 stratify it based on what we know about medically and  
11 not report of the clinical symptoms, but based on more  
12 objective evidence of, you know -- for instance, like  
13 the enzyme activity of the protein and the genetic  
14 mutation underlying the disease and the protoporphyrin  
15 level, the biochemical certain serum markers and  
16 biomedical markers to define the disease a little  
17 better in order to stratify this population.

18           Maybe we'll understand the disease a little  
19 sooner. Just like in cancer biology, you know, it's  
20 difficult to treat every single melanoma patient the  
21 exact same way, and there's some common pathways. But  
22 they're also very, very different.

1           So develop these tools to better define the  
2 population and the diseases that we're studying I  
3 think is extremely important as well.

4           DR. BALWANI: I think it's very difficult to  
5 have risk stratification in this disorder. It's very  
6 well recognized that genetic disorders present across  
7 a spectrum. So we want to be able to develop a  
8 treatment which can address patients across a disease  
9 spectrum, not just stratify and develop disorders for  
10 those at highest risk.

11          DR. TENG: Exactly. I agree. I think that  
12 there needs to be that balance, you know, targeted  
13 therapy versus a broad treatment for symptomatic and  
14 clinical improvement. Yeah.

15          DR. DESNICK: We've looked at -- we've  
16 genotyped over 250 people with EPP. It's a cortical  
17 recessive disease. We've also looked and published on  
18 XLP, which is a very rare form of X-linked, you know,  
19 erythropoietic porphyria. It manifests probably a  
20 little more severe but in males because it's X-linked.

21          But to make a long story short, we've never  
22 been able to correlate anything other than proto



1 levels with severity. It's not about the mutations.  
2 It's not about the low expression wheel. It's  
3 probably 25,000 other genes that relate to the  
4 production of protoporphyrin or its stability or its  
5 entrance in and out of the mitochondria, or whatever.

6 So we don't really understand severity in  
7 this disease. We know that with every genetic  
8 disease, there is a range of variability. Some people  
9 burn in two minutes, and some people burn in more than  
10 a half an hour. And that's just the tingling prodrome  
11 we're talking about, not the extensive pain.

12 So I think it's very hard to try and  
13 strategize anyway. We want to develop a drug that's  
14 good for every single patient.

15 DR. EGGERS: So Maureen, did you want to  
16 make a comment? And then we'll -- I think we're just  
17 making -- we're going to be weaving a lot in a pretty  
18 organic conversation here.

19 DR. POH-FITZPATRICK: Well, protoporphyrin,  
20 I think I would agree with my colleagues, is a  
21 disorder with a great deal of natural variability.  
22 There's a lot of difference in protoporphyrin levels

1 and pigmentation of the skin and thickness of the  
2 stratum corneum and latitude at which you live and  
3 whether it's a rainy season or whether you're ambient  
4 humidity tends to be dry. There are a lot of  
5 variations -- whether you're a person who likes to be  
6 outdoors, doesn't like to be outdoors.

7           What we do know as much as we can about some  
8 quantifiable value related to the pain or reaction  
9 that's gotten -- I would agree with Dr. Desnick -- is  
10 that there is some relationship between a very low  
11 porphyrin level and a very high porphyrin level and  
12 the likelihood that you'll have lesser  
13 photosensitivity or greater photosensitivity.

14           But it's not a mathematical kind of  
15 relationship. There are all these other variables  
16 that weigh in so much that it's very, very difficult  
17 to control for all those confounding variables and  
18 designing any mathematically defined outcome.

19           DR. EGGERS: Okay.

20           DR. POH-FITZPATRICK: So what I think I've  
21 heard this morning from so many of the patients here  
22 is that they know very well what their problem is.

1 And if you listen to many of them, you can really get  
2 the same story pretty much.

3 It's the pain. It's that deep pain. It's  
4 the unremitting pain. It's the pain that's  
5 indescribable because there's no language equivalent  
6 to it. And then you hear stories about, well, we did  
7 this drug or that drug or whatever. And we know that  
8 we were doing better.

9 With all these variables and ages and  
10 pigmentations and latitudes and whatever, that is the  
11 criterion that I think is the most compelling, is that  
12 these folks know when they're doing well and when  
13 they're not.

14 And they have a whole construct of what they  
15 have to do to get them to be able to sort of live.  
16 They're alive. They've very alive. They're here, but  
17 their lives are so constricted and so constrained by  
18 all this stuff that it's really important, I think,  
19 for all of us to try to think together on a way of  
20 getting them so they can lead a life that's worth  
21 living to the extent that most of us can lead a life  
22 that's worth living.

1           So what can we do about that? Well, we can  
2           try to do the best we can with these clinical trials.  
3           There have been several of them now. I think the  
4           endpoints are kind of vague, at best, except for the  
5           big criterion, is do the people who have done it  
6           believe convincingly to those who listen to them that  
7           there is a difference when they're using whatever  
8           method they're using to relieve this pain. And I  
9           think that's the best criterion that I can listen to.

10           DR. EGGERS: Okay. Yes. Go ahead.

11           (Applause.)

12           DR. MARCUS: So --

13           UNIDENTIFIED FEMALE SPEAKER: (inaudible -  
14           off mic).

15           DR. MARCUS: Can -- yes, listening to the  
16           patients is very important. And you know, as a  
17           regulator, I'm still trying to quantify it.

18           And I would just like to acknowledge that --  
19           you know, I believe you talked about the heterogeneity  
20           of the disease. And I believe Michael has 1 minute,  
21           and other people may have slightly more than 20  
22           minutes.

1           So please understand from the perspective of  
2 a regulator, for a product that gives you an  
3 additional five minutes in the sun, that will be  
4 transformative for Michael, who has one minute. That  
5 will actually be a difficult difference to measure in  
6 somebody who's got over 20 minutes.

7           But we need to figure out a way that we can  
8 measure the impact for both people. And this is where  
9 -- yes, we can listen to the patients. But in the  
10 end, we're regulators, and we have regulations. And  
11 we also have to try and design a clinical trial that  
12 can convincingly demonstrate an impact such that we  
13 can take an action.

14           And so I'm saying that, in order that you  
15 understand, I believe we should be listening to you.  
16 I'm just helping -- trying to help us have a dialogue  
17 in a language and in a manner that we can all come  
18 away with what we need, all of us.

19           Does that make sense to people? No?

20           (Crosstalk.)

21           UNIDENTIFIED MALE SPEAKER 9: All of our  
22 levels aren't the same all the time. Our porphyrin

1 levels are different. The UV lights are different.

2 The outside index is different.

3 DR. MARCUS: Right. So this is challenging.  
4 So this is a challenging conversation to have. So one  
5 thought that I'm having in having this dialogue today  
6 -- and I'm going to say all this, and I cringe a  
7 little because my patient reported outcomes colleague  
8 on the end of the table, Dr. Papadopoulos, may cringe  
9 when I start throwing this stuff out because patient -  
10 - you know, there is a method to patient-reported  
11 outcomes.

12 But for me, if -- you know, in just talking  
13 to people today and having read your -- you know, the  
14 letters that I've gotten, you know, if you start out  
15 with a list of activities that range from walking from  
16 my house to the mailbox, walking from my car to a  
17 store, driving to work, taking my child to the park,  
18 watching a one-hour soccer game, those are increments  
19 of time that are meaningful to you.

20 And so it may be meaningful for one patient  
21 to go from being able to walk to the mailbox to being  
22 able to walk from the car to the store or being able

1 to drive to work. Those are meaningful incremental  
2 benefits to you that aren't necessarily -- that are  
3 more meaningful, frankly, to me than a five-minute  
4 incremental benefit because it speaks to the quality  
5 of life gained for you. And I understand very small  
6 increments of ability to tolerate the sun translate  
7 into huge quality-of-life changes for you.

8 But we need to be able to -- and this is I  
9 think where we're all struggling. I -- we hear you,  
10 but we need to be able to put that on paper. And to  
11 me, just talking about those activities is very clear.  
12 But we've been measuring minutes -- you know, small  
13 minutes of benefit, and that's much harder. And maybe  
14 I just need to tell you that. That's much harder than  
15 actually just saying I can walk from the car to the  
16 store now. But we have to measure that even in a  
17 systematic way in order to be able to demonstrate  
18 efficacy.

19 So I've gone on for too long.

20 DR. POH-FITZPATRICK: Let me just add about  
21 photo-provocation testing, which was a question.  
22 Having tried to do it in protoporphyria patients with

1 a fairly good understanding of the natural history of  
2 the disease and photobiology and wavelengths of light  
3 and machinery and filters and so forth and so on, I  
4 found it to be extraordinarily difficult, almost  
5 uninterpretable, in the long run. So I would tend to  
6 lean away from trying to use that as a quantitative  
7 criterion for all of the variable confounding factors  
8 that were described.

9           If some way could be a measure developed as  
10 you're suggested to determine the impact factor on  
11 individuals' improvement with or without any  
12 treatment, that could be mathematically, statistically  
13 analyzed in such a way that you could get some kind of  
14 a semi-quantitative number to quantify the impact on  
15 100 different, 200 different patients, considering  
16 what their ordinary baseline value would be and then  
17 after the treatment or during the treatment, what that  
18 impact factor turned out to be. And that would be up  
19 to the statistical experts to design that query.

20           DR. EGGERS: We'll let -- okay. Elisabeth,  
21 please.

22           DR. MINDER: I do not agree. I think the



1 variability is so large between these and the patient  
2 also has a priming phenomenon (ph). And we have so many  
3 influences we cannot control for them.

4 But I think what is best is integral to what  
5 we have measured in the Phase III trial. That is a  
6 total number of sun exposure without pain. There you  
7 have a statistical significance difference between the  
8 patient on placebo and those on active. And I think  
9 if you look at that, that it's much better than any  
10 average on day. But you cannot use it an average on  
11 day because on average on day it's subject to a lot of  
12 variation.

13 But if you take the integral for four months  
14 or six months so you have probably a rather adequate  
15 measurement because the variation say are equally  
16 distributed during this time. And so we have a  
17 statistically significant effect in the U.S. trial.

18 It -- the patient increased their time in  
19 the sun without pain for, I think, one-third or one-  
20 half. So they have a really strong increase in the  
21 sun exposure time. And I think this is just what  
22 translates. Also variation -- and I think that the

1 best measurement we have. We will not find anything  
2 which is better than that.

3 (Applause.)

4 DR. BEITZ: Dr. Minder, if I could follow on  
5 to understand a little bit better, you've presented  
6 information about pain-free time in the sun. There's  
7 a challenge, as has been expressed not only by the  
8 patients, but also by the experts in their  
9 presentations with the variability of the disease.

10 You've mentioned yourself, or perhaps  
11 others, the seasonality to the disease. Some have  
12 mentioned -- and I'm going somewhere with all these  
13 caveats and rambling. There is going to be a  
14 question.

15 Some have mentioned -- Dr. Desnick, I  
16 believe -- that there may be a correlation between  
17 porphyrin or protoporphyrin levels and disease  
18 severity. Those can vary from patient to patient.  
19 Are there -- were we hypothetically to use time --  
20 what was it -- time -- pain-free time in the sun, were  
21 we to look at that as an endpoint, are there other  
22 things that we should control, maybe not formally

1 stratify -- possibly stratify for or analyze for?

2 Does the design need to take into account  
3 season unless you're doing a full-year trial? Does  
4 the design need to stratify or analyze based on  
5 baseline porphyrin levels? Are there -- help us with  
6 other things that may, whether that endpoint or a  
7 different endpoint, are there things that we can do in  
8 the trial or in the analyses that could help us.

9 DR. MARCUS: I just want to make one more  
10 comment in this conversation. And I get the sense  
11 that the conversation we're having is that you're  
12 saying we have statistical significance. And what  
13 we're saying is help us come up with clinical trial  
14 designs moving forward.

15 So I don't want to imply in any way that we  
16 are ignoring the findings of alfa melanotide trial. I  
17 do want us to focus on forward thinking so that we are  
18 convincingly able to demonstrate an impact on -- for  
19 example, my goal would be in a rare disease. You  
20 know, what can we show with 10 patients? What can we  
21 show with 20 patients?

22 We need -- I think we can -- I'm not willing

1 to say we've got the best endpoint that we're going to  
2 have, but that's me. I don't want to stop at one  
3 solution, and as I've mentioned already --

4 UNIDENTIFIED MALE SPEAKER 6: The first  
5 step.

6 DR. MARCUS: What's that?

7 UNIDENTIFIED MALE SPEAKER 6: It can be the  
8 first step.

9 DR. MARCUS: Absolutely, and I'm not saying  
10 that it's not. But I'm trying to have a broad  
11 conversation.

12 UNIDENTIFIED MALE SPEAKER 6: (inaudible -  
13 off mic).

14 DR. MARCUS: Right.

15 UNIDENTIFIED FEMALE SPEAKER: You can't  
16 prevent bullying? I mean, that's what we feel like.  
17 I mean, have you ever been out there and been bullied  
18 as an adult or as a child --

19 DR. MARCUS: I -- we should -- I understand,  
20 and I --

21 DR. EGGERS: The microphones.

22 DR. MARCUS: I'm really trying to use this

1 time to help us think about clinical trials. This is  
2 not a statement about any -- the state of any drug  
3 development program by wanting to be forward thinking.  
4 It's not commentary on what's been done already.  
5 That's all. And that's really all I can say.

6 But I just -- I think that there has to be a  
7 certain amount of -- I don't know a better way to say  
8 it, and I -- believe me, I understand the frustration.  
9 I understand your suffering.

10 I can't truly understand it because I  
11 haven't lived through what you all have lived through.  
12 I can certainly --

13 UNIDENTIFIED FEMALE SPEAKER: You have to  
14 pass it on to a child.

15 DR. MARCUS: I understand all that. I mean,  
16 I hear you. But we're really trying to focus on -- as  
17 I said, pediatric clinical trials in this disease,  
18 which is already rare, might be a trial where you've  
19 got 5 patients, maybe 10 patients. And what can you  
20 do to convincingly demonstrate an impact and determine  
21 a safe dose?

22 And so I think we can do better than pain-

1 free time in the sun. We've already talked about all  
2 the complexities and variability in patients. And it  
3 seems to me an activity is fairly easy to demonstrate.

4 Just one that's come up today of being able  
5 to walk from a car to a store. I think that's a  
6 significant impact. I think that might be something  
7 that's readily measured in 5 to 10 patients. But I --  
8 again, I cringe when I say that because this is a  
9 collaborative effort with everybody in the room.

10 I'm thinking about paths forward, and that's  
11 where I -- you know, I've already thought about ways  
12 that this can be done. And I really would like some  
13 help, and that's what you're here for.

14 (Applause.)

15 DR. MARCUS: And I'll just say one last time  
16 this is not commentary on anything that's already  
17 transpired.

18 I've been the division director of this  
19 division for two years, and I'm bringing a new  
20 perspective to our division. And I'm trying to  
21 accomplish many tasks simultaneously, and this is one  
22 of them, trying to create paths forward. And it would

1 be great if we could all work on that.

2 DR. EGGERS: So then just as the moderator,  
3 do we want -- do you still want your -- Jill, do we  
4 want to go to your question or move on?

5 UNIDENTIFIED FEMALE SPEAKER: (inaudible -  
6 off mic).

7 DR. EGGERS: Okay. Then you can respond.  
8 What comes to mind when you're hearing this?

9 DR. DESNICK: You know, I would also like to  
10 see better endpoints -- endpoints that are more  
11 robust, endpoints that really are convincing.

12 The problem is twofold. If you're measuring  
13 viral load and protease inhibitors, you've got  
14 laboratory data that you can really measure. In this  
15 disease, you -- we don't have a target of proto  
16 because the proto levels didn't change in any of the  
17 studies. And we don't have a target of measuring  
18 increased enzyme activity. These are the two basic  
19 path -- this is the basic path of physiology of why  
20 they have this disease.

21 And until we have targets like that, I don't  
22 think, because of the inherent nature of the disease

1 and the fear of having pain, that we're going to be  
2 able to develop the kind of robust measures you want.

3 In fact, if you look at the data from the  
4 trial that we did do, both European and U.S., we found  
5 that most of the patients, whether they were in the  
6 placebo group or they were in the treated group, still  
7 feared going out in the sun. And that's why the  
8 measurements that we got were so low.

9 And that's why the differences are not  
10 robust because nobody wanted to get burned. They have  
11 this inherent fear so ingrained from the first time  
12 they -- who got laid up from being burned when they  
13 were a kid that all they do all day is work a  
14 schedule, as you heard Dr. Poh say, to make sure they  
15 can get through the day without getting burned. And I  
16 think that's the inherent problem because most of us  
17 at this table have thought how do we do it better.  
18 How would we do it better?

19 At first, we thought maybe it was photo-  
20 provocation. But then we learned that it's like  
21 radiation, that you build up a level. And if you come  
22 on your bike or you get exposed to the sun and you get



1 a baseline level that's elevated, it's different from  
2 time to time. And that's too variable. It doesn't  
3 allow for any objective measurement.

4           When we talk about other ways of doing it,  
5 there isn't a device that would allow people to wear  
6 it, like a child, and go around and measure the  
7 intensity, the wind, the weather, the humidity, all  
8 these kinds of things, and integrate that into chill  
9 factor, if you will, or a pain factor. And I think  
10 until we have such instruments, it's going to be very  
11 hard to do this.

12           And I think we all struggle with the exact  
13 same question you're answering, and I wish that we  
14 could come up with a better -- I'm not wed to any  
15 particular trial endpoint. If there was something  
16 better, we should try it. But until somebody really  
17 comes up, I don't know.

18           And I will tell you that in the study that  
19 we did do, the small amount of difference that we saw  
20 was, in Europe, significant. In the U.S., it was .04.  
21 And that doesn't reach -- that's -- you know, that's  
22 great, but it's not what you'd like, like .001. And

1 that would be convincing.

2 And I think that until we can think of a  
3 better way -- and if you have some ideas, you should  
4 share them with us because we've dealt with these  
5 patients. And the patients are all here, and maybe we  
6 can work out something together.

7 I really worry about how we can get these  
8 kids into a small trial, like you suggest, that will  
9 be meaningful and allow you to do more than safety.

10 And that -- and the only other thing that is  
11 convincing to me, I must say, is that there are people  
12 here who have gone three to six times to see Dr.  
13 Minder. There are people in Italy and Belgium and  
14 Switzerland, the report of Minder with 107 patients  
15 where there was very little -- you know, if they got  
16 pregnant, they stopped for a while. If they came for  
17 a long distance or whatever it was that they couldn't  
18 do or if they had to be at work, they were -- you  
19 know, they didn't get the drug. But the rest of them  
20 have been on drug continuously for --

21 DR. MINDER: For up to eight years.

22 DR. DESNICK: -- up to eight years. And to

1 me, that -- you know, being a physician, when somebody  
2 comes back and back and back, it must be doing  
3 something meaningful because it's an effort.

4 DR. LINDSTROM: Thank you so much. You've  
5 raised a lot.

6 And I want to move away from the results of  
7 a particular trial to a question that has come up, in  
8 my mind. And I'd love to hear how you utilize  
9 laboratory measures in your care of patients.

10 So protoporphyrin measures, are those  
11 something that are -- that you measure and follow?  
12 And again, don't read anything into this. My question  
13 -- I'm -- it's a question. I want to know how you use  
14 those levels.

15 And then I have a separate question. In  
16 fact, I'm going to lay it out here, but maybe you can  
17 address one fully and then address the second. I'd  
18 also like to hear from you because we have this unique  
19 talent pool right now.

20 I'd like to understand. People have said  
21 that photo-provocation doesn't work. And I'd like to  
22 hear a little bit more about that with regard to --

1 and you mentioned a UV device, almost like a  
2 radiometer that folks wear to measure, you know, X of  
3 radiation and so forth.

4 But my question comes from both of those. I  
5 believe it was Dr. Minder, perhaps Dr. Lim, mentioned  
6 that there may be multiple wavelengths involved, the  
7 short band, the higher visible lights. UV may be  
8 provoking in some subsets of the patients.

9 In light of the potential variability in --  
10 or potential spectrum of wavelengths that may be  
11 involved, can you also speak to how that might impact  
12 photo-provocation, positively or negatively, whether  
13 it could be used and whether -- how that would impact  
14 monitoring devices? The first question is more  
15 important.

16 DR. EGGERS: So before you get to those two  
17 questions, just a time check. Do we have open public  
18 comment signup?

19 MS. CHALASANI: We do.

20 DR. EGGERS: Okay.

21 MS. CHALASANI: The full 10 minutes.

22 DR. EGGERS: The full 10 minutes. Okay. So

1 we have then another, we'll say, 10 minutes to have  
2 this facilitated discussion. So maybe briefly answer  
3 Jill's two questions, and then we'll ask for one final  
4 question.

5 DR. LINDSTROM: First, monitoring use of  
6 porphyrin levels in your -- clinically.

7 DR. BALWANI: I can respond to that. So as  
8 part of our consortium, we try to develop guidelines  
9 for monitoring patients. And we do monitor  
10 protoporphyrin levels annually. We find that it often  
11 doesn't correlate very well because there is some  
12 variability in protoporphyrin over time.

13 But we do like to monitor them  
14 longitudinally to see if there's an indicator. For  
15 instance, if we would see a significant jump in the  
16 protoporphyrin level, we would certainly be concerned  
17 about liver disease.

18 Some of the other parameters we measure are  
19 hemoglobin, hematocrit. We measure your iron profile.  
20 We measure vitamin D levels, liver function tests for  
21 patients. So those are our standard monitoring  
22 annually for all of these patients.

1           And I'll let Dr. Poh-Fitzpatrick or Dr.  
2 Minder talk about photo-provocation.

3           DR. POH-FITZPATRICK: Okay, I will. I agree  
4 with Dr. Balwani. That's how laboratory standard  
5 tests are used in monitoring patients with  
6 protoporphyria, chiefly looking for changes in the  
7 protoporphyrin level going higher, which would suggest  
8 then you were having a liver problem, looking at the  
9 liver function tests to see whether or not that is  
10 borne out, you know, pursuing liver studies and so  
11 forth.

12           Plasma porphyrin may be going up. Stool  
13 porphyrin may be going down. And that's understanding  
14 the natural history of the disease and using these  
15 parameters in a clinical sense to take care of each  
16 individual patient.

17           We almost never use photo-provocation  
18 testing in normal clinical work. This is only a  
19 research type of procedure. And I understand that  
20 some photo-provocation testing was done on areas that  
21 have been light exposed chronically over time and  
22 probably have been exposed to light coming and going

1 and over the last week -- was it rainy, was it sunny,  
2 whatever -- which would have put a very large variable  
3 factor load on any result that you might get.

4 Using photo-provocation on an area that's  
5 more sun protected would be a better risk. But still  
6 having done that, I can tell you that it may be very,  
7 very difficult to reliably do it reproducibly day  
8 after day after day, even under the best of  
9 circumstances. So we generally don't use it much for  
10 anything, really.

11 DR. LINDSTROM: Would any of you see any  
12 merit to stratifying by protoporphyrin levels?

13 DR. POH-FITZPATRICK: In the sense that you  
14 could probably expect that individuals who have a  
15 lower protoporphyrin level toward the lower end of the  
16 spectrum, someone who has a level that tends to run  
17 around 300, maybe some 250. Maybe someday it's 400 --  
18 somewhere around there would probably be less  
19 photosensitive on average than an individual whose  
20 protoporphyrin level tended to vary between 3,000,  
21 2,500 and 4,000. They would probably be much more  
22 photosensitive.

1           But on the other hand, one might have a  
2 whole lot more pigment and have some natural  
3 protection. So there are many things that would  
4 factor into what you can use, changes in  
5 protoporphyrin levels to predict about level of  
6 photosensitivity.

7           And then all the other confounding variables  
8 -- what's their life like? Do they go out? Don't  
9 they go out? What's it like where they live? Do they  
10 -- you know, there's just so many things to try to  
11 control for that I think it's virtually impossible.

12           Going forward and testing new things coming  
13 down the pipeline, looking at things like  
14 protoporphyrin levels, if there is something that  
15 actually does change the protoporphyrin level by  
16 either affecting the pathway, facilitating conversion  
17 to protoporphyrin, fixing the enzyme somehow and  
18 giving the new enzyme, doing things that would  
19 actually change the dynamic equilibrium of  
20 protoporphyrin manufacturer circulation and excretion,  
21 there you could use those kind of numbers as  
22 endpoints, understanding that there's going to be a



1 certain variability that you just have to factor in.

2 DR. LINDSTROM: Of course.

3 DR. MINDER: So just can I say something?

4 DR. LINDSTROM: Thank you.

5 DR. MINDER: We have a continuous  
6 distribution in the protoporphyrin levels. It's some  
7 skewness. It's not a symmetric distribution, but it's  
8 a continuous. We don't have subgroups, which we could  
9 identify.

10 And we have no connection with genetics. In  
11 Switzerland, we have a relatively homogenous  
12 population, so we have repeated the same mutation.  
13 and we could not find any correlation to the mutation.  
14 So it's just -- we don't have subgroups. And we don't  
15 -- also, we don't have subgroups in the clinical  
16 symptoms.

17 It's really continuous. We have patients  
18 who have less symptoms, but it's -- we cannot -- a  
19 group is less symptoms. A group is high symptoms.  
20 It's just a continuous between low and high symptoms.  
21 So -- and we cannot identify. Protoporphyrin has some  
22 effect, but it's not the effect, what we find.

1 DR. EGGERS: We're going to go with Dr.  
2 Balwani, then Dr. Lim real quickly. and then Dr.  
3 Beitz has a final question.

4 DR. BALWANI: So just again to reinforce  
5 what everyone said, in our analysis of our patients in  
6 the Porphyria Consortium, we have about -- data on 226  
7 patients. And we did see a correlation with  
8 protoporphyrin levels and time to bond.

9 It's the first time we were actually seeing  
10 a correlation with high protoporphyrin-level patients  
11 having more severe symptoms. Again, there are a lot  
12 of caveats to this, as Dr. Poh-Fitzpatrick discussed.

13 DR. DESNICK: If you look at the data from  
14 that study that we don't want to talk too much about,  
15 the ones --

16 (Applause.)

17 DR. DESNICK: -- please --

18 (Applause.)

19 DR. DESNICK: -- the ones that had the most  
20 effect, the longest in the sun, it was almost curative  
21 for them because they almost normalized. And they  
22 were the mildest patients.

1           So when you start thinking about which way  
2 you're going to go, if you're going to pick the most  
3 severe, they may get X amount of benefit whereas the  
4 others are going to get even more. And I think one  
5 has to think through. We don't want to label with any  
6 EPP drug that says your protoporphyrin level has to be  
7 X. And that's why I think most of us feel that  
8 looking at the whole population is the right way  
9 rather than --

10           (Applause.)

11           (Crosstalk.)

12           DR. POH-FITZPATRICK: The intent was  
13 stratification, not label.

14           DR. MARCUS: Right, stratification as a  
15 means of controlling for that confounding variable in  
16 order to better demonstrate the treatment effect.

17           And I guess I'm willing, again, in terms of  
18 I understand that traveling, you know, one of the  
19 factors that patients reported as important is whether  
20 participation in the clinical trial would require  
21 travel. I understand that there can be cost and  
22 travel constraints to participating.

1           And so if we can identify a subpopulation --  
2   you know, if a trial can be enriched with the  
3   population, as you said, actually the milder patients  
4   who have a more dramatic effect, it may take fewer  
5   patients to meaningfully demonstrate benefit.

6           And you know, labels describe the clinical  
7   trials under which a product is studied. You know, I  
8   think it would be upon us to discuss whether a  
9   subpopulation can adequately demonstrate benefit  
10  across all of the population and make that  
11  extrapolation for an indication, describing the  
12  clinical trial in the label, you know, that was used  
13  to demonstrate that.

14           DR. EGGERS: Dr. Lim, did you want to say  
15  something?

16           DR. LIM: Yes, just a brief comment about  
17  the photo-provocation testing. The action spectrum of  
18  porphyrin is in a visible light range that measure  
19  four from 400 on up. Up to now, there had been very,  
20  very few light sources that contains only pure visible  
21  light.

22           There are now light sources that can be used

1 that contain only pure visible light. We have done a  
2 number of studies on that, not for porphyria. But --  
3 so theoretically, there would be one that can be used.  
4 But again, we don't have any data right now.

5 And those light sources right now, the  
6 irradiation field is still very, very small. So if we  
7 need to do that, we have to modify to see if we can  
8 irradiate a large area to try to reproduce the  
9 symptoms. But again, I just do not have any data on  
10 that.

11 DR. EGGERS: So I'm going to -- just for the  
12 sake of time, I know some people have to travel at  
13 4:00 o'clock. Then the last panel question will come  
14 from Dr. Beitz to be answered. And then we're going  
15 to move into the public comment session.

16 DR. BEITZ: No, just a question about  
17 extrapolating efficacy from adults to children. I was  
18 wondering what your thoughts were. If you had a  
19 treatment that was efficacious in a 25-year-old, what  
20 are your thoughts about saying anything regarding  
21 efficacy of that same product in a 5-year-old or a 12-  
22 year-old? Do you think it's realistic that we could

1 extrapolate the experience in older individuals down  
2 to younger?

3 DR. EGGERS: Why don't we start with --

4 DR. BEITZ: This is for efficacy now.

5 DR. EGGERS: Dr. Balwani, do you want to --  
6 okay.

7 Dr. Minder?

8 DR. MINDER: Actually, as of genetics, it's  
9 about the same in the children less (ph), and as in  
10 all of (ph) I don't see a difference. So I don't see  
11 that there should be -- that there is any -- speaks  
12 anything against to extrapolate. I think children  
13 have usually, in my experience -- I'm interested what  
14 my colleagues say, but children usually have a little  
15 bit lower protoporphyrin levels.

16 And the protoporphyrin levels increase  
17 during puberty. But on the other hand, the children  
18 have very thin skin. So they are also very sensitive.  
19 So I think this balance for the lower protoporphyrin  
20 level. So I think children may react really the same  
21 as adults on the drug.

22 DR. EGGERS: Add on that, Dr. Balwani?

1 DR. BALWANI: Yeah, I would agree with that.  
2 I don't see any reason we cannot extrapolate the  
3 results from adults to children. I do think children  
4 will get a benefit.

5 DR. EGGERS: Okay.

6 (Applause.)

7 DR. BALWANI: And I just also wanted to  
8 mention that it would be great to have good quality of  
9 life indicators in the pediatric population. I think  
10 we are really lacking that, and that's a very  
11 significant point to capture.

12 DR. EGGERS: Final comment? Or Dr. -- two  
13 final comments.

14 DR. POH-FITZPATRICK: Okay. Well, I would  
15 just say that in having treated quite a number of  
16 pediatric patients with protoporphyria, their skin is  
17 indeed are probably somewhat thinner. Their  
18 protoporphyrin levels varied all over the place just  
19 the same as adults.

20 They -- the impact on their lives is  
21 probably even greater than that on adults, who the  
22 parents do a wonderful job of trying to make a life

1 for them. But I think anything that we can do to make  
2 more -- to expedite any arrangements for being able to  
3 translate an agent that is approved in adults to the  
4 pediatric population, particularly with this disorder,  
5 which is so devastating to childhood, would probably  
6 be a worthwhile thing to do.

7 And the flexibility and judgment that is  
8 accorded to the FDA by statute would seem to be great  
9 criteria to apply in this situation.

10 (Applause.)

11 DR. EGGERS: Dr. Teng, did you have a final  
12 comment?

13 DR. TENG: I'm just commenting on -- along  
14 the same line that for children, that besides, you  
15 know, the regular stuff that we all appreciate other  
16 things like attention deficit in school performances  
17 and just some of the psychiatric impact. It can  
18 probably be considered into some of these endpoint  
19 measurement as well.

20 Other things that a couple of people in the  
21 audience have pointed out that, you know, for  
22 instance, a bone fracture, risk of fracture and bone



1 density, you know, questions that we may not know at  
2 this point. So those are the things, and maybe, you  
3 know, can be quantifiable and, you know, their vitamin  
4 D and the calcium and all that.

5 DR. EGGERS: Okay. So with that, we're  
6 going to close the scientific portion.

7 A couple things -- please leave your  
8 clickers on the table. We've had people think of them  
9 as souvenirs before, but please leave them on the  
10 table.

11 This discussion has opened up a number of  
12 complexities. There's still the public docket. We  
13 didn't get to go out in the audience and ask for  
14 patient comments on much. You managed to give your  
15 thinking, I think, very well through the applause of  
16 the various comments that were made by the experts up  
17 here.

18 But we do -- if you have thoughts on  
19 clinical development or clinical trial design, please  
20 share those with them because, even though it wasn't  
21 said out in a public forum like this, the comments are  
22 all coming to us and they are important. We want to

1 hear your perspective for that.

2 Evaluation forms -- please fill them out and  
3 let us know how we're doing. We learn something every  
4 time, and we use the feedback we get to make our  
5 meetings better.

6 So with that, I'm going to turn it over to  
7 Pujita Vaidya.

8 MS. VAIDYA: Hello everyone. I'd like to  
9 thank you all for coming today. We've had very rich  
10 discussions, and now we're moving into the open public  
11 comment session.

12 I just wanted to let you know that we will  
13 not be responding to your comments, but they will be  
14 transcribed and be part of the public record.

15 So we have 7 people who have signed up, and  
16 we have 10 minutes for each person -- for the whole  
17 session. So each person will get a minute and a half.

18 So what I've done here is the light -- this  
19 will turn on when your minute and a half starts. When  
20 it turns yellow, it will -- you will have 30 seconds  
21 left. And then once its red -- I would like to  
22 apologize right now -- I will need to ask you to

1 please stop, and then we'll have to move on to the  
2 next speaker.

3 So I'll run through the order of speakers.  
4 If you could all line up right up here on the right.  
5 We have set up a mic over here. And then we can get  
6 started. So first, we will have Michael Olscher,  
7 sorry. We have -- and I apologize in advance if I  
8 mispronounce your name.

9 We have -- next, we have Desiree. Then we  
10 have Olivia Donahue (sic), Vickie Lewis, Julianna  
11 Amodei, David Garrett. And then finally, we have  
12 Jasmin Barman. Sorry, if I mispronounce your name.  
13 Okay.

14 UNIDENTIFIED MALE SPEAKER: Jasmin.

15 MS. VAIDYA: Oh, Jasmin. Yes, Jasmin  
16 Barman. Sorry.

17 Okay. So now we can get started. So first,  
18 we have Michael.

19 MR. OLSCHER: The day's been informative for  
20 you. I just want to stress that what a difference  
21 even five minutes would make to my life as far as  
22 walking with my head up from a car to a bank, not

1 worried about what people might be thinking or having  
2 the police called on me just because I've got a hoodie  
3 on and I look suspicious. That would be just drastic  
4 for me, to be able to walk anywhere really and hold my  
5 head high instead of looking down.

6 And lastly, I basically just want to address  
7 the younger people and the children and let them know  
8 it does get better. It does get easier. People will  
9 bully you no matter what. I think if you're  
10 different, they'll pick on you.

11 So you have one life. Do what you can. If  
12 you can cover up and that works for you and you're  
13 worried about what other people think, don't. Just  
14 cover up. Get out there. Enjoy life no matter what  
15 happens with drugs. I try not to get my hopes up, so  
16 you just deal.

17 So don't let it hold you back. If you can,  
18 get out there. Ignore what everybody says about you  
19 because, really, it's your experiences that matter.  
20 So go live your life. That's all. And thank you.

21 (Applause.)

22 MS. VAIDYA: Thank you, Michael.

1           Next, we have Desiree.

2           DESIREE: Thank you again for this  
3 opportunity. I know all of us are grateful. I'd like  
4 to speak for the patients who had to work and couldn't  
5 be here and who couldn't be on the web today. And  
6 they would have me say to remember these things.

7           First off, many of them told me that when  
8 they did the trials, the clinical trials for  
9 alfamelanotide, some of them waited until they were  
10 halfway through to even test it. It took them that  
11 long to step their foot out the door. They were  
12 thinking about it.

13           Secondly, they said to remember that fear is  
14 a great motivator. Love is the greatest motivator,  
15 and I think it's love for these children and love for  
16 one another is why so many people came, not just for  
17 themselves but for one another. But fear is a great  
18 motivator, and that fear is very prevalent in  
19 everyone, as you have heard.

20           And in designing a trial, of course, we're  
21 hoping that you're talking about another trial and not  
22 repeating the trials that we've already done because

1 they expressed they wouldn't be willing to do that.

2 But in new trials and for these children, that is also  
3 going to be very important because they are developing  
4 this same fear.

5 MS. VAIDYA: Thank you, Desiree.

6 (Applause.)

7 DR. EGGERS: Next, we have Olivia.

8 MS. DONAGHY: Hi. I'm -- my name is Olivia,  
9 and I'm 10 years old.

10 I just wanted to say that the pain is worse  
11 than anything you've ever felt. There's no word to  
12 describe it. You will do -- with EPP, you will do  
13 anything you can to get away -- to avoid the pain.

14 When I was four and I was having one of my  
15 first reactions before I was diagnosed, I -- in my  
16 sleep, I was banging my hands against the wall because  
17 it felt better. So also, I'm guilty because my  
18 brother loves to go outside and play. And I'd love to  
19 join him, but I can't.

20 (Applause.)

21 MS. VAIDYA: Thank you.

22 Next, we have Vickie. Yeah, come on Vickie.

1 Oh, you can come on up.

2 MS. AMODEI: Hi. I'm Julianna Marie Amodei,  
3 and I'm 11 years old. I'm from Syracuse, New York,  
4 and it took until last year for me to get diagnosed  
5 with EPP.

6 During the last six years, we have -- we had  
7 to leave many family vacations due to a reaction. We  
8 have been to many different specialists. My mom saw  
9 the Dateline show, and she asked the dermatologist to  
10 order a blood test for EPP. And my hands and feet,  
11 they burn and sting. And my nose gets really patchy  
12 whenever I'm having a reaction.

13 And whenever I want to go out to outdoor  
14 camps or sports, I have to say no. But I think that  
15 with Scenesse, I could say yes.

16 (Applause.)

17 MS. VAIDYA: Thank you, Juliana.

18 And then next we have Vickie -- Vickie  
19 Lewis. Okay.

20 Okay. So we'll move on to David Garrett.

21 MR. GARRETT: Hi. I'm David Garrett. My  
22 birthday was yesterday, and I'm older than 10 now.

1 (Laughter.)

2 MR. GARRETT: I just wanted -- and it goes  
3 more to the trial. In passing, it was mentioned a  
4 minute ago about vitamin D levels. As it happened,  
5 when I was in the Stage 2 -- the Phase II trial and  
6 had the active drug, I overlapped twice with my  
7 regular doctor and checking my blood. And she was  
8 surprised because I actually had higher -- much higher  
9 than for me and higher than the midrange of vitamin D.

10 Since then, I'm now up to 10,000 IU a day  
11 just to keep it at the minimum level. It might be  
12 something you can look at because all of us, we don't  
13 get sunshine at all. We just -- there's no way to go  
14 the simple way.

15 And I actually had a visiting doctor one  
16 time comment on my vitamin D and say, well, this is  
17 simple. Just go outside every day for 25 minutes --

18 (Laughter.)

19 MR. GARRETT: -- without sunscreen, and  
20 you'll be better. You'll feel better.

21 The second thing is I did the trial, and it  
22 wasn't a matter of even just hours a day. It was the



1 whole day that I could be in the sun. I had maybe one  
2 time at the end of the trial on the very end of the  
3 pellet where I was slightly burned.

4 I really want a BMW convertible before I  
5 die.

6 (Laughter.)

7 MR. GARRETT: You're really in the way, and  
8 you're stopping that. So if you could step it up  
9 before I go away so I can buy it.

10 (Laughter.)

11 (Applause.)

12 MS. VAIDYA: Thank you so much, David.

13 And finally, we have Jasmin.

14 MS. BARMAN: Hello. I just wanted to add  
15 two thoughts. One is in the trials, pain-free days  
16 really (ph) should. But it's likely an  
17 underestimation of the real value because, for us  
18 patients, also less pain matters and, also, when the  
19 symptoms resolve faster, what we also experienced.  
20 That was the first thing.

21 The second thing is that we heard that it's  
22 about clinical trial design for kids. And I just want

1 to say that we just heard how hard it is to measure  
2 the efficacy in adults. Then we heard that it's  
3 unethical to put patients, EPP patients, in the  
4 situation to expose themselves to this kind of pain.

5 And we also heard that patients, also kids,  
6 discontinue treatments which are unsuccessful. So I  
7 can say for myself, I had antihistamine. I had iron  
8 therapy. I had beta-carotene. I had sunscreens. I  
9 put this in the bin because it wasn't working.

10 So one suggestion could be to just measure  
11 treatment outcomes -- treatment adherence as treatment  
12 outcome in kids because it's a special situation.

13 Thank you.

14 MS. VAIDYA: Great. Thank you, Jasmin.

15 (Applause.)

16 MS. VAIDYA: And finally, we have a quick  
17 announcement from Desiree.

18 DESIREE: Those who are on the bus, I'm  
19 sorry, but we're going to have to leave right now --

20 MS. VAIDYA: Okay.

21 DESIREE: -- because the bus is leaving.

22 MS. VAIDYA: Okay.

1           DESIREE: And please forgive us, but if  
2 you're going --

3           MS. VAIDYA: Okay. We have --

4           DESIREE: Thank you again very, very much.  
5 We sincerely appreciate it.

6           MS. VAIDYA: Thank you.

7           We have a quick, final comment from Dr.  
8 Marcus, so I'll call her up.

9           DR. MARCUS: I realize you all have to  
10 leave, so I'll just be brief. This has been of  
11 tremendous value to me, and I hope that no one walks  
12 away today feeling like their efforts have been in  
13 vain.

14           As I opened this morning and I will close  
15 now, I really am in awe of you, of the efforts that  
16 you went to, to come today and of the incredible  
17 challenges that you face on a daily basis to do things  
18 that I take for granted.

19           And I think all of us here have learned a  
20 tremendous amount and can use that knowledge to move  
21 treatment for this disease forward.

22           So thank you again, and safe travels.

1 (Applause.)

2 (Whereupon, the meeting was concluded at

3 4:31 p.m.)

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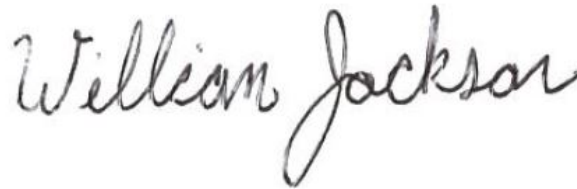
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