

**UNITED STATES DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Food and Drug Administration**

**FDA CBER OTAT Patient-Focused Drug Development
Listening Meeting**

November 15, 2022

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MS. ANNE ROWZEE: Hello, everyone. Thank you all for joining us for our patient-focused drug development listening meeting. Today's event is hosted by Office of Tissues and Advanced Therapies, or, as we usually say, OTAT for short, within the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration.

My name is Anne Rowzee. I am an Associate Director for Policy in OTAT. I will also be your host for today's event. I'm pleased to welcome you all here today as we hear from patients, caregivers, advocates, and others on their understanding and expectations regarding gene therapy products, including cell-mediated gene therapy. This event, in part, meets an FDA commitment; it's part of the sixth reauthorization of the Prescription Drugs User Fee Act, also known as the PDUFA VII.

As you all know, this is an important and exciting time in the gene therapy space, and we appreciate all of you for joining us for today's event so we can hear your perspectives on these products. We expect that the remarks from today's speakers will generate additional ideas and comments. If you have a thought or a comment you'd like to share, we encourage you to submit those to the docket, which is available on regulations.gov. The docket will remain open until December 15. The number is FDA-2022-N-2394.

We have a full agenda plan today. We'll kick off today's meeting with opening remarks from Dr. Wilson Bryan, Director of OTAT. He'll share more of FDA's regulatory oversight of gene therapy products. We'll then provide an overview of the meeting process and then move into the listening portion of the meeting. Today's four sessions will be on the following topics:

- Session 1: patient and caregiver understanding and expectations of gene therapy risk and benefits.
- Session 2: patient and caregiver involvement in clinical study design and execution.
- Session 3: current tools and methods to capture patient experience data and any existing challenges or gaps to capturing patient experience data.
- Session 4: approaches to leverage existing tools or opportunities for unique tools to capture patient experience data in gene therapy studies.

This event is being recorded. The recording will be posted on FDA's website in the next few weeks. Closed captioning for this event is available directly on Zoom. Lastly, as another reminder, please direct any comments related to the subject

matter of today's meeting to the docket and only use the chat box if you're experiencing technical difficulties.

With that, I'm going to turn it over to Dr. Wilson Bryan for today's opening remark.

DR. WILSON BRYAN: Thank you, Anne, and good afternoon, everyone. I am Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, or OTAT.

Welcome to our patient-focused drug development meeting on gene therapy products. We are very glad that you have joined us today. As Anne mentioned, our goal today is to hear your perspectives on gene therapy as patients, caregivers, and advocates. Your insights into what it's like to live with a medical condition or care for someone with medical condition can directly inform research, working to develop new treatments and help the FDA in our evaluation of a product's safety and effectiveness.

Let me begin by talking about who we are. Within FDA, the Center for Biologics Evaluation and Research, or CBER, regulates vaccines, blood and blood components, allogeneic, plasma protein products, cellular therapies, and gene therapies. OTAT's mission is to promote public health through a collaborative, science-based process to ensure that medical products are safe and effective. In doing so, we strive to make all regulatory decisions based on rigorous data within partiality and compassion. Our focus today is on gene therapy products.

Many of you are attending today's meeting because you, a loved one, a family member, or a friend have some knowledge about gene therapy. But for those who are new to the field, let me provide a brief overview. Every cell in your body has a copy of your DNA. Genes are a specific section of that DNA. Different cells can express or use different combinations of genes, depending on the role of that particular cell in the body. In gene therapy, scientists can do one of several things, depending on the problem that is being treated.

If a particular gene is causing a medical problem, then scientists can turn off that gene. If that gene is causing that medical problem, scientists can repair that bad gene so that it no longer causes a problem or, as an alternative, scientists could replace that bad gene that causes a problem with a new gene that doesn't cause a problem. They can turn off the gene, they can repair the gene, or they can replace the gene. In other cases, scientists can add a new gene to help the body fight or treat a disease. Gene therapy can be administered in a number of ways. One of the most common ways of administering gene therapy is by using vectors such as viruses to deliver pieces of DNA to the body.

What makes gene therapy so exciting is the possibility to address serious medical conditions that have few or no other treatments available. As new therapies are developed and tested, regulatory oversight is essential to ensure that these new gene therapy products are safe and effective for patients. FDA's regulatory oversight begins with clinical trials which test products in development to ensure that

participants' safety and rights are protected. FDA also works with researchers and scientists to provide guidance on the design of clinical trials, as well as to verify the integrity of trial data. FDA then performs a rigorous review of the study results. FDA monitors products before they come to market and continues to monitor products after they are on the market to ensure quality throughout the products' entire life cycle. FDA also advances the state of the science by providing guidance and education to product developers. Finally, stakeholder and patient engagement are critical aspects of our work. We communicate with patients, caregivers, and advocates to improve our understanding of patient needs, and we collaborate with drug developers to make sure that products are designed to meet those patient needs.

We are seeing incredible progress in the field of gene therapy. OTAT has approximately 1,000 gene therapies in clinical trials. While there is still much to be learned about rare diseases, we do know that about 80% of rare diseases are caused by a single gene defect. Gene therapies to treat diseases that are caused by single-gene defects could mean improvement in survival and quality of life for patients. There are currently four FDA-approved gene therapies for single-gene disorders. And two of those products were approved this year. But we cannot cure and treat difficult diseases without your help. Patients, patient advocates, and caregivers have an important role in advancing gene therapies. OTAT is committed to finding ways to work with patients and their families, who are often experts in their diseases.

This is exactly why we are here today. We want to hear about your experiences as patients and caregivers so that we can support the design of clinical trials which incorporate your priorities and develop new gene therapies that meet your needs. We want to learn about your expectations regarding the risks and benefits of gene therapy. This can include what meaningful benefits patients expect from gene therapies. What risks are patients willing to tolerate as part of a treatment? What preferences and priorities do patients have when they receive treatment and when they decide between treatment options? We want to hear what patients and their families think about when they consider participation in a clinical trial involving gene therapies.

Because FDA provides oversight of clinical trials, we want to understand the challenges of participating in clinical studies. We also want to hear your perspectives on the risks associated with participating in clinical trials. We are looking for your feedback on the tools currently being used in clinical trials to capture your experiences. We want to hear if there are any existing approaches that could be leveraged more effectively or opportunities for new or unique tools that are not currently being used in gene therapy studies. This will help ensure that your perspectives, needs, and priorities are meaningfully incorporated into the development and evaluation of new gene therapies. Gene therapy has much to offer, and OTAT believes that patients will be the driving force for new scientific advancements.

Finally, I want to share a few ways that you can stay in touch with CBER. In the coming months, OTAT will provide educational resources and host webinars about topics related to gene therapies and other regenerative medicines. For the latest information on gene therapy and other regenerative medicines, please visit our website. You can sign up to receive email updates from us and subscribe to our newsletter.

Thank you all for being here today.

MS. ROWZEE: Thanks so much, Wilson. We're now going to move into the public comment portion of today's meeting. Before we hear from our first speaker, I'd like to give a brief overview of the meeting process. During this event, all microphones for the general audience have been muted. Because this is a listening meeting for FDA, we will not be addressing questions from the audience. As Wilson has said, we do appreciate your comments, and we encourage you to go to the docket if you'd like to share specific feedback for today's topic on what you've heard today.

Speakers, we greatly appreciate your interest and your willingness in speaking at today's meeting. Please remain muted until I call your name. I will introduce each speaker so that you can begin your presentation or remark. You'll be notified and asked to unmute yourself at that time. Once your presentation is finished, you'll be asked to go back on mute and allow the next speaker to present. For those of you who have submitted slides, your slide presentations have been added to this master slide deck. When speaking, please let us know when to advance the slides on your behalf.

Please state your name and your affiliation at the beginning of your presentation. To ensure transparency, we encourage you to advise the audience of any financial relationship that you may have with any firm, groups, company, or products at the start of your presentation. If you do not have a financial relationship as such, please make a statement to that effect. Please keep the time limit in mind when speaking. We will give you a 30-second notice before your time is over so that you may then wrap up your presentation. If you run out of time, again, we encourage you to submit your remaining comments to the docket.

Lastly, each session is going to end with an opportunity for FDA to ask clarifying questions of the speakers. I'd like to take a quick moment to introduce our subject matter experts from OTAT who are serving on today's panel. First is Dr. Najat Bouchkouj, who's a medical officer at the Malignant Hematology Branch. Dr. Jasmine Gatti is a clinical team leader in General Medicine Branch 2. Dr. Elizabeth Hart is branch chief of General Medicine Branch 1. Dr. Yuxia Jia is a medical officer in the Oncology Branch. Dr. Larissa Lapteva is associate director in the Division of Clinical Evaluation and Pharmacology/Toxicology. Thank you so much for our panelists for your time today.

We're now going to start with Session 1, and the topic for the first session is patient

and caregiver understanding and expectation of gene therapy risk and benefit. We have 22 speakers for this session, and each speaker will have 4 minutes. I'd like to remind our speakers to please stay online after you speak and for the duration of this session in the event that our FDA panelists have clarifying questions for you at the end.

Our first speaker is Kim Stephens.

DR. STEPHENS: My name is Dr. Kim Stephens, and I'm the president of Project Alive. I represent the Hunter syndrome community or the MPS II community. We are very focused on gene therapy right now. It is one of the available clinical trial treatments in our community. One of the things that I always stress is that our patients know the risks. Right now, there is no treatment available — FDA-approved treatment for the cognitive impact of Hunter syndrome. So the boys have a progressive disease. They are going to lose their ability to talk, to walk, to communicate. And so we realize that gene therapy is not a cure. We certainly have been very good about communicating that with our community, letting them know that damage is already done from the time that the child is born and it's a progressive disease again. But our expectation for gene therapy is to certainly give back some of the enzyme that the boys are missing. So that is our hope. And our hope is also that it would get to the brain, but also to the body, to some of the areas that enzyme replacement therapy doesn't reach. And again, the benefits really, for most of us, outweigh the risk. With the progressive disease, we know that the natural history for our boys: Around 2 or 3, they're going to start to decline, they're going to start to lose their speech, they might end up in a wheelchair, and then obviously passing away usually before the age of 15.

So I just encourage the FDA to approve more of these gene therapies. To see that there are thousands of gene therapies in trials right now is wonderful. I'd like to see that number of the ones that are approved grow in the next year, because, again, we have so many families with rare diseases that are waiting, like our Hunter syndrome community, for an approved drug, so thank you.

MS. ROWZEE: Thank you so much, Kim. Our next speaker is Allyson Berent.

DR. BERENT: Thank you so much. I'd like to thank the agency for giving me the opportunity to speak on behalf of our community on the Foundation for Angelman Syndrome Therapeutics. My name is Allyson Berent. I'm the chief science officer for FAST, as well as a veterinarian, and I'm the mother to this beautiful little girl on the right. Her name is Quincy. She's 8 years old, and she lives with Angelman syndrome. I don't know if I've noted your disclosures related to this one, but I'm a paid consultant to Ultragenyx Pharmaceutical.

Angelman syndrome is associated with profound symptoms and a significant clinical unmet need with no approved treatments currently. The symptoms of Angelman syndrome, as a monogenetic, nondegenerative neurodevelopmental disorder, include

the universal lack of speech, significant and severe debilitating seizures, ataxia in coordination, profound sleep disturbance where individuals can sleep 2 or 3 hours a night, and the impact that it has on a child, on their family, is tremendous. These kids can have significant feeding issues and GI issues, and most importantly, they cannot live an independent life, but they live a normal length of life. There is a major impact on the family, including the inability to hold employment; significant depression, anxiety, and stress; significant loss of sleep; and financial impact and the quality of life this can have on relationships and families can be quite tremendous.

We decided to host a focused group on gene therapy for Angelman syndrome in support of this forum. We did a semi-structured group survey in order to assess the attitudes toward gene therapy for Angelman syndrome. In a brief background we gave on in vivo versus ex vivo gene therapy so the audience and the families could really understand the difference as we work very hard to educate our community. The focus group included 29 individuals from 23 states and 3 Canadian provinces. And then we did a post-group survey and that included 13 responses. The demographics of those individuals included the median age of diagnosis of the children to be 1 year, ranging between 6 months and 6 years, with the current patient age at the time of this forum of 8 years, ranging between 2 and 25 years. The demographic of the genotype included 84% being deletion, 8% mutation, and 8% having imprinting center defect.

Through that education and really understanding the caregivers' need for knowledge, we asked them, after we gave them a small lecture about what is gene therapy in vivo and ex vivo, "Will education be crucial to helping to make decisions about the future impact that the gene therapy could have on your child?" The answer was universally, 100% yes. After that forum, they felt very comfortable being closer to be able to make decisions like that. One answer that a parent gave was, when we asked, "How did you know about gene therapy before this focus group?" is that we know "enough to be dangerous, but this got me thinking about a lot of other factors that I haven't considered." Another question was, "Did you learn something from this focused group that was unclear to you before?" The answer is universally yes. Overall, one comment was "It was informative to learn...at a very basic level behind scientific acronyms and the descriptions, understanding clinical trials. I learned about the differences between in vivo and ex vivo gene therapy and how they can carry different risks." Understanding that in Angelman syndrome, we have eight current programs using AAB gene therapy, two in IND-enabling studies. We have one program with a lentivirus hematopoietic stem cell gene therapy. That's an IND-enabling study. We have three ASMs in the clinic and five CRISPR programs. It's very important that our community understands risks and benefits.

Through this open discussion, we asked a bunch of questions: "What are some of the most important considerations you would have in deciding to give a gene therapy treatment to your loved one with Angelman syndrome?" And really, what the most

important risk were, understanding — “what are those theoretical risks? How effective is it? How long will this last? Can it be repeated, or is it ‘one and done’? And is it reversible or irreversible?” When we asked, “Does your decision of enrolling in a clinical trial for a gene therapy impact you if you think about the fact that if you enroll in the trial, there would be less cost potentially than if you were to wait for an approval?” the answer was, only 25% felt that money would have an impact on that.

A majority of parents were not willing to do a gene therapy if the trial would include a placebo control arm or a sham control. And overall, 69% would not be interested if there was a sham control, and 61% would not be interested if there was a placebo control.

“Would you attempt a gene therapy if it was FDA approved?” The answer is markedly yes.

In conclusion, the AS community is excited about gene therapy and feels that education on risk/benefit is incredibly important. They trust patient advocacy groups. Enrollment in a trial involving the sham or placebo will be challenging and should impact the success of trials. You need to think about that carefully as we think about how we design trials. But once a gene therapy is approved, the willingness to receive that therapy was incredibly high. Thanks, everybody, for your time.

MS. ROWZEE: Thank you, Allyson. Our next speaker is Suzette James. Suzette, are you on the line?

I don't think we have her online. We're going to move on to our next speaker, Aviva Rosenberg.

MS. AVIVA ROSENBERG: Thank you for having me. My name is Aviva Rosenberg. I am the co-founder of the Gaucher Community Alliance, United States, and I'm on the executive board of the International Gaucher Alliance. For our gene therapy project that the IGA undertook, we received corporate sponsorship from Sanofi, Pfizer, Takeda, AVROBIO, and Prevail. I don't receive any personal compensation from this.

Gaucher disease is a lysosomal storage disorder. There's two types; There's the non-neuronopathic, which is the type that I have and my family has, and then there's the neuronopathic Gaucher disease, which affects the cognitive and neurological systems. There are currently no FDA-approved treatments for the neurological Gaucher disease. What the International Gaucher Alliance wanted to do is, we wanted to understand what our community knows about gene therapy. There's several current clinical trials in both the United States and around the world, and there's many more on the horizon, so it's really important to us to understand what the community knows about it, what they think about it, and their willingness to

participate in trials. This study is a two-prong approach. We first had focused groups in the spring of 2021 and followed that with an international survey in the spring of this year.

We had three focus groups that were professionally facilitated. The first group is parents and caregivers of those with Gaucher disease type 2 and 3. This is the neurological form of the disease. The second group was young adults living with neurological Gaucher disease, and the final group are individuals with type 1 disease, which is the Gaucher disease that does not affect the neurological system. We had participants in these focus groups from the countries listed. So it was a very nice representation, although we'd love to have more.

Like the last speaker, there were similar themes emerged on the focus groups, although it did suggest that those affected by Gaucher disease generally share some common views. The people wanted to understand gene therapies — what were the risks; what were the benefits, the life limitations, the side effects; is it a one-and-done or is it — will they have to continue to get treatment. And those who were more educated and those with children that had more advanced symptoms were both receptive to the possibility of gene therapy.

Following up the focus groups from those responses, we developed an international survey based on that, and it was validated with a number of IGA members. After the survey was finalized, it was live for a month and a half and had over 100 responses from individuals from around the world. We then engaged a medical data analytics company to both help us design the survey and to analyze the results. The survey conclusions, which we're very happy about and we have put with — they're under analysis, and they're submitted for review for publication by Orphanet, which hopefully will be very early in the next year. The reason behind this whole project was really to focus our ability to program and educate the community. And so, based on the responses from both the survey and the focus groups, we're now in the time frame for designing our programming.

This was our project. And so, as we're waiting for the publication to be reviewed and accepted, we're also engaging in our educational activities. The educational activities are really going to be based on the type of targets we have, whether we're targeting adults, young adults, older adults. Different people have preference for different type of educational activities, whether they're live, in-person webinars; animated — and this was all covered in the survey. So I think we've got some really good responses about how to go, what the best way for educating the community based on where they're at, to understand gene therapy and their willingness to participate in clinical trials or after approval.

Thank you very much for listening and thank you for the work.

MS. ROWZEE: Thank you so much. Our next speaker is James Rippy.

MR. JAMES RIPPY: My name is Jim Rippy. I'm with severe hemophilia, and I had gene therapy about 3½ years ago. And so, I have no financial conflicts of interest for this outside of participating in gene therapy. You get a small stipend for visits. A little bit different topic than I was expecting. I didn't know it was to be understanding and expectations. However, I spent approximately a year studying virology, immunology, and gene therapy before I decided to pursue gene therapy. I think it's very important, from a patient's standpoint, to understand what you're getting into. The type of gene therapy that I was participating in — it's one and done in a number of ways. It's one treatment, but also, if that treatment doesn't work, you're not likely to be able to try again for that form of gene therapy. I think it's very important to the patients to spend plenty of time understanding what they're getting into. I think if I hadn't done my own homework, I may have been disappointed. But like I said, I spent over a year studying this.

The first gene therapy I applied for I did not get in, based off some lab work. But then I was contacted about 3 months later and got into a program using a different vector. I had very good outcomes, which is nice to hear. My clotting level went from 1 to 2% up to an average over the last year of 29%. So, basically all my bleeds, spontaneous and injury bleeds, have disappeared. But it's so important to understand the risk/benefits and I understand there are different types of gene therapy, which may not disqualify you from a second treatment. But in my particular case, that was very important to know.

As far as a burden on your life, I spent probably the first period of time right after probably three to six months had people coming to my office and drawing blood on a regular basis, two or three times a week. I think that's important to understand, but it wasn't nearly as burdensome as just regular treating of hemophilia. I didn't really find that there was much burden during the clinical trial process. The risk/benefits — once again, I had studied that, so I pretty much knew — I even took a course in virology and immunology, just to make sure that I was up to speed before making such an important decision.

I do think it's very important to self-educate. I believe if the FDA or whoever is performing the clinical trial could basically come up with reading materials, support materials — I did all mine, learning online, self-driven. But I think that is an incredibly important thing to know once you're starting this process.

As far as unknown risks, I really don't think that I've subjected myself to any unknown risks. I pretty much read all sorts of gene therapy cases about people having minor problems, no problems, even leading up to death. It's just important to understand what you're getting into and maybe even set a time limit on how much time you need to pursue understanding the topic, understanding the treatment process before you get into it. I hope that's helpful. But I did my homework, so I was very pleased with the process and studied all my treatment options. I looked into probably about five or six different gene therapy products before I made my

decision.

MS. ROWZEE: Thanks, Mr. Rippy. I'm going to move on to our next speaker, Jennifer McNary.

MS. JENNIFER MCNARY: My name is Jenn McNary. I have two young adult sons living with Duchenne muscular dystrophy. I have no relevant financial relationships to disclose. As many know — and I won't spend a lot of time — Duchenne is a fatal muscle-wasting disease that begins to show up in symptoms in early toddlerhood and ends in death from teen to early adulthood. Along the way, it takes away the ability to walk, lift arms, and eventually to breathe on their own, among other symptoms.

My son Max has been incredibly lucky to be at the right time and age and place since he was a young toddler. His older brother, just 3 years older, has not been as lucky. I've had the privilege to have a front-row seat to watch the science in Duchenne literally involved and improved since February of 2002, when my two sons were diagnosed, when we were told there was no hope and to take them home and love them. They were going to die. Max isn't part of making that history. I've come to know that the way that we battle Duchenne is with early access to innovative therapies: access to deflazacort, at 2 years old, imported from Canada but now approved in the U.S.; access to EXONDYS 51 via a clinical trial at age 9 but now approved in 2016; and last summer, access to gene therapy through a small clinical trial that included nonambulatory patients. Because Max had access to steroids to reduce inflammation, he was eligible and still walking when exon skipping came along. Exon skipping then slowed the progression greatly and kept him walking until he was 17 and a half, which is unheard of. It kept his lung function stabilized. And so, he was one of the oldest patients able to participate in a gene therapy dosing at age 20.

Today, at almost 21, Max is stable. In fact, at 21, he is able to get in and out of his own bed. He will be ordering groceries online today and opening his apartment door while I'm across the country to bring them in and put them away. He'll be making all of his meals alone and feeding himself. He'll be letting his dog outside to play. And for him, the benefit of gene therapy is more independence at an age that it's incredibly important to him.

Max is stable in his disease progression because he had early access to cutting-edge science and his body still had muscle to preserve. It didn't matter that he had lost the ability to walk when he got gene therapy. He's still making use of his upper body strength and, of course, his breathing as well. Unfortunately, Austin continues to be just a few years and a little bit of muscle loss too late for clinical trials, and he'll again be waiting for approval, for access.

When it comes to gene therapy in Duchenne, being the mother of an older and more advanced patient, our tolerance for risk is incredibly high. I know what's happening

without intervention, because I see it every day in our community. These young men pass away at alarming rates. My expectations are realistic. I believe that having access to gene therapy early, before muscle loss, produces a much higher benefit, of course, as with any intervention. But I also believe as long as there is muscle to preserve, there is value in doing so.

I would really appreciate any dialogue that the agency wants to have with our community and with the others here today to better understand our perspectives, our tolerance for risk, and our appreciation for early approvals even in gene therapies. Thank you.

MS. ROWZEE: Thank you. Our next speaker is Luke Rosen.

I don't think we're seeing Luke on the participant list. We're going to move to our next speaker, Veronica Hood.

DR HOOD: Hi, my name is Dr. Veronica Hood and I'm the scientific director for the Dravet Syndrome Foundation. I do not have any financial relationships to disclose, and I just want to thank you for the opportunity to speak today on behalf of families living with Dravet syndrome.

Dravet syndrome is a rare disease characterized by severe, medication-resistant seizures, as well as impacts on many other developmental processes, such as behavior, cognition, movement, sleep, and growth. There's also a 20% risk of premature mortality, often related to sudden unexpected death and epilepsy.

Notably, the majority of cases are caused by haploinsufficiency of the *SCN1A* gene, which proof-of-concept studies have shown can be addressed by a variety of genetic therapy approaches, some of which are entering clinical trials.

In February, the Dravet Syndrome Foundation, or DSF, held an externally led, patient-focused drug development meeting specifically for Dravet syndrome to gather input from the community about aspects of living with Dravet syndrome and needs for future treatments.

From that meeting, polling showed that most caregivers feel current treatments are not adequate and have many drawbacks, including side effects and lack of efficacy. DSF ran a supplemental survey with this meeting, where we got over 100 responses from caregivers, gathering information on perspectives related to genetic-based disease-modifying therapies. As far as symptoms they want to see addressed, seizures, of course, rose to the top, but you can see from this graph that there is a preference for a large number of other symptoms to be addressed by these therapies.

We went on to delve deeper into caregiver perspectives on when they would consider a genetic-based therapy under varying levels of invasiveness for administration, going from IV administration to a lumbar intrathecal dose or directly to the brain. We also asked about permanency, whether it's repeated dosing or a one-time permanent treatment. And then under each of those scenarios, we asked

about whether it only treated seizures or seizures and other symptoms. This graph to the right is an example of the somewhat complicated output from each of these questions, and if you'd like to see this in full, you can visit dravet-el-pfdd.org and find the full survey within the appendix of the *Voice of the Patient* report.

What I will tell you today are just a few of the major takeaways from that, which is that 98% of caregivers were interested in a genetic therapy on some level of either invasiveness and benefit, showing that there is really a very high need for improved treatments for this population and they're willing to risk new therapeutic approaches. Unsurprisingly, you might be able to see in this graph, if we're just going from left to right, from the least invasive to the most invasive and more permanent therapies, there is a slight shift; you'll see higher green bars in the percentage of caregivers that would consider that therapy if it only was shown to possibly either treat seizures or seizures and two-plus other symptoms. When you move to the more invasive and permanent options, you start to see that caregivers really want to have more evidence to suggest that there will be a definite major benefit either to seizures or to seizures and other symptoms. I think, though, what's notable from this data is that 63% of caregivers would consider a one-time injection directly to the brain — so the most invasive and permanent option — as long as seizures were definitely addressed, and 83% would consider it as long as seizures and two other symptoms were addressed. I think this really shows that there's an immense disease burden in this community. That balances against the potential risks for caregivers in making these decisions.

The last thing I just wanted to end on was just really thinking through, making sure that we're measuring, in clinical trials with these therapies, things that really, truly impact quality of life for families, more than just pure seizure counts.

And with that, I'll just leave you with my contact information and where you can find more insight on what I've presented today. Thank you.

MS. ROWZEE: Thank you. Our next speaker is Tushar Tangsali.

MR. TANGSALI: Hi, so my name is Tushar Tangsali. I have two boys with Duchenne muscular dystrophy. Neil is 11; Nevan is 7. Neil was diagnosed when he was 4 years old in 2015. Nevan was diagnosed in 2019. Both of them have long deletion 8 to 25 in the dystrophin gene, which is in the early part of the gene, where there is not enough research happening, according to me. I've been attending a bunch of conferences, following a lot of research, and coming up with strategies to improve my kids' life. Even with the same mutation, what has happened is, both boys have followed a different path. Neil was ambulatory until last year, until he was 11, but Nevan lost his ambulation right after he turned 7. We know that this progression in each boy, even for the same mutation, is significantly different.

Some points I would like to make to FDA: expanding the trial requirements — for example, ensuring that all segments of the Duchenne population — and again, thank

you, Jennifer McNary, for giving an overview of what your boys went through. We need to ensure that all segments of the patient community are included in these trials. For example, just including a 4 to 7 cohort for ambulatory patients and 8-plus for nonambulatory patient doesn't really help a lot of families, because there are patients out there — there are families out there with kids who are in the 4 to 7 range, but they are nonambulatory or who are in the 8+ age range, but they are still ambulatory. We need to form the trials or cohorts — would be arranged specifically to address the parents' and kids' needs so that we can extract the most benefit of it.

The other thing is, we need to ensure that the principal investigators and the hospitals included in these trials are clear about what constitutes what are the trial requirements. For example, if there is a cohort added for, let's say, nonambulatory, then the principal investigators and hospitals should treat all nonambulatory kids in the same bucket and not pick and choose kids who have lost ambulation in the last 6 months or last 9 months just to improve the chances of research.

The second big point I would like to bring forward to FDA is improving response to the clinical holes in case of serious adverse events. I understand that these events have to be monitored, but we need to improve the protocol to improve the response so that the trials can be restarted, because for a lot of families, for a lot of parents, a lot of patients who are eagerly looking forward to these trials — the whole, if it drags on for, like, 6 months or 9 months, may not seem like a big time, but these 6 months, 9 months, 12 months is when the muscle can reduce drastically to a degree where there is significantly less chance of improving even after we get those improvements.

The third and the last point I would like to make is, when a trial is analyzed and the results are deemed as statistically significant or not, please try to understand that the parent perspective. If FDA rejects a drug, saying that it is not statistically significant, even though it has visual benefits, try to understand the patient and the family perspective, because getting some benefit now can improve the quality of life for the next 5, 10 years, which, again can extend the lifespan from 20 to 30, which, can, in turn, give the kids a chance of a miracle happening, let's say, 5 or 10 years from now. So that's how I would like to have FDA revisit the statistically significant clause. Thanks for having me.

MS. ROWZEE: Thank you. Our next speaker is Shandra Trantham.

MS. SHANDRA TRANTHAM: Hi. My name is Shandra Trantham. I'm a patient with Friedreich's ataxia and a PhD candidate, and I have no financial disclosures. So FA, or Friedreich's ataxia, is a rare genetic disease caused by hindered production of a protein called frataxin. Lack of frataxin is detrimental to many areas, including the CNS, PNS, heart, and pancreas. Patients like me experience progressive neurological dysfunction, losing the ability to walk, speak, hear, see, and live independently, and eventually die of cardiac complications. I was diagnosed at 12,

and now at 25 I can't walk without a walker. I also deal with painful falls almost every day, and I've been through major surgeries to manage complications of the disease.

The ideal therapy for FA would address all aspects of this multisystem disease and totally reverse symptoms. We understand how big and currently unrealistic that ask is. Therefore, we would like gene therapy trials to provide patients with the best shot at benefit, least risk, and possibility to participate in future trials after gene therapy administration. We know that gene therapy may only be designed to treat one area instead of every affected tissue. Additionally, we know that gene therapy may only stop progression rather than reverse symptoms, and it may not even do that. Patients still want these drugs developed. We expect that FA will be treated by a cocktail of medicines, and we believe that gene therapy will be an important part of this cocktail.

Because of the permanency of a gene therapy treatment, there are additional risks that we are aware of, and we will carefully weigh these with potential benefits on an individualized level. With the increased risk, we are extremely grateful for the FDA's guidance to industry on gene therapy that puts our safety first. However, we have concerns with the guidance for gene therapy for neurodegenerative disease that recommends a staged approach to early-phase treatment by unilateral injection. We would like the FDA to consider that not all areas of the brain function perfectly bilaterally.

One such area is the dentate nucleus of the cerebellum, an important treatment target in FA. The circuitry of the cerebellum is complex, in that some pathways cross to a synapse on the other side of the brain and some do not, meaning that each cerebellar hemisphere affects both sides of the body to some degree. It follows, then, that unilateral treatment will not result to restriction of effect to one side of the body and its image results; both sides of the body may be afflicted. If the treatment works, there is potential for the partial or mixed nature of this effect to cause even more dysfunction to balance.

We know that this guidance is intended for safety such that unilateral treatment would prevent the loss of function of an entire bilateral structure if damage occurs. Unfortunately, in the case of FA and the dentate nucleus, unilateral treatment will not result to a unilateral effect. It actually has the potential to worsen a patient's neurological function. We find the risk posed by unilateral treatment to be unethical and unacceptable, even for the handful of patients in an early-phase trial. We ask that the FDA reconsider this guidance in the context of intraparenchymal CNS treatment for FA. Thank you.

MS. ROWZEE: Thank you. Our next speaker is Robert Rydberg.

We're going move on to our next speaker, Richard Poulin.

MR. POULIN: My name's Richard. I've received paid honorariums to talk about AADC deficiency. I also received payment to do a call about AADC News through online publication known as BioNews. My wife and I are teachers in Thailand, and that's kind of supported what we've done to start our nonprofit organization called Teach RARE. Based on some of the conversation that's already happened, I would like to restructure my presentation, but I just look forward to the FDA continuing these types of discussions. It's been great hearing everyone speak before me. But I'm going to adapt my presentation and just speak a little bit more about what some of the other presenters have talked about today.

Our goal is to support families. But one of the issues for our disease that our daughter has, known as AADC deficiency, is that there's only about 130 of us. There's not too much attention, obviously, for this, other than through our small groups and talking to our families. The mortality rate, where our daughter is facing death — and the average rate is between 4 and 7 years old. We had no family history. The birth was normal. It came to us as a shock, as I'm sure other families that have autosomal recessive diseases like AADC deficiency. But we did begin to see some signs, and that parent intuition kicked in, and we brought our daughter to the hospital.

It's important to consider before gene therapy what life was like for us, because the effects of after gene therapy has just been miraculous, to say the least. But what begins is a journey of misdiagnosis for just about everyone in our community. That misdiagnosis ranges, but usually, epilepsy's the first; we're often confused with cerebral palsy, dystonia, and other types of procedures — diseases. But eventually, you get to a point where the doctors probably just say you don't know.

And so what happens is you go through this battery of testing — and because of the disease, our daughter has high anxiety, but she's also just a baby, so being in a hospital is not the most fun thing for a baby, and we're prodding her with needles, spinal taps, putting her into CT scans, genetic testing, all of which come back inconclusive for our rare disease, which doesn't help us get any information about what's happening to our daughter.

We want to get information — we have to deal with our daughter's screaming and going through pain. It usually results into sedating our child to try to get some of this information. She's in through a lot of anxiety and pain. If we're not admitting her to just do these routine tests, we're strapping her down or holding her down just so the doctor can get blood. And even though we've had misdiagnosis and/or tests came back inconclusive, parent intuition kept kicking in, telling us that there was something more to this.

And what we saw, we had called spells and doctors had called seizures — in hindsight, are known as oculogyric crises. It's very painful, but this was one of the things that stopped us from trying to do intervention, which I would like to speak

more about later, but one of the things that has helped us receive some of the great effects and maximize the full potential of gene therapy is early intervention, the intervention that happens before gene therapy and the intervention that happens afterwards. But if you think it's seizures, then you're not doing any type of intervention, because as parents, we were worried that we were inducing the seizures and possibly creating brain damage.

All of us that are considering gene therapy hope to minimize, if not get rid of, the symptoms of our diseases. For us, it's known as oculogyric crisis. It happens every 3 days, it lasts for hours. Our daughter is twisting her limbs, crossing her eyes, tongue thrusting. The only time we ever saw movement was during these episodes, and it's just very scary, and there was nothing that we could do.

The only thing we could do is just record the data, go to the doctor, and say, "Hey, this is what we're seeing," and they would come back with "inconclusive" or "not sure."

It's also important to note that, as we're searching for answers before gene therapy, trying to figure out what this is and how can we treat this, our daughter is going in regularly for these emergency visits into the pediatric ICU for various reasons, and so we were always in the hospital. We were faced with so many medical bills in addition to trying to pay for testing. We had to hire outside help, because my wife and I had to keep our jobs as teachers, so it's not the biggest salary, and trying to keep our daughter alive, trying to get answers about what was happening to our daughter.

And through all this, we were not sure how to proceed. With gene therapy, all of that disappeared. Our daughter is now independent, she is not into ICU. She's never been back to the hospital. She's walking, she's swimming, she's jumping. She's talking. We are teaching her multiple languages.

I just wanted to end with that: that there is a pathway to maximizing the potentials of gene therapy and that we shouldn't discount the expectations of gene therapy or what the symptoms are saying, even cognitive, because we've been able to grow past that. Thank you for listening to my comments.

MS. ROWZEE: Our next speaker is Eszter Hars.

DR. HARS: My name is Eszter Hars. I'm the president and CEO of the Shwachman-Diamond Syndrome Alliance and a mother of a child with Shwachman-Diamond syndrome Alliance, or SDS for short. Thank you very much for the opportunity to speak today, and I have no financial disclosures. Our focus is really around the prevention of catastrophic cancer in Shwachman-Diamond syndrome patients.

SDS is a rare, heritable genetic disorder that affects the protein production in every

cell of the body and affects every organ system, but in particular, or it's particularly problematic for the bone marrow. It causes a very high risk of developing leukemia — about 1 in 3 patients by age 30 — and it's almost universally fatal. The leukemia is almost universally fatal in SDS patients.

Today, patients face frequent blood draws, infections, bone marrow biopsies, and also dealing with other organ system issues, such as digestive issues, growth, and skeletal systems. But what is most prevalent or unifying within our community, I would say, is the constant fear of when leukemia would strike our loved ones.

Two years ago, we started the Shwachman-Diamond Syndrome Alliance, specifically focused on driving research towards a cure for Shwachman-Diamond syndrome. And in the context of this discussion, a cure for us means to prevent the progression to leukemia. If other symptoms are improved as well, that would be a win and desired, of course.

So, SDS is a great candidate for gene therapy, because the genetics is well understood. The most patients have mutations in one particular gene, the *SBDS* gene, and within the gene, the mutations are very uniform as well. Almost all patients have one particular mutation that they have in common, so that should help us drive gene-targeting therapies forward — both *in vivo* gene therapies in the future and *in vitro* gene therapies probably in the nearer term, where hematopoietic stem cells can be taken out of patients; fixed, so to speak; and then infused back into patients, targeting the bone marrow or the hemopoietic system.

We are interested in all sorts of gene therapy, not just fixing the genome itself, but other types of therapies that act on a genetic level. Our patient population has a good understanding that this is a genetic disorder, and addressing the issue at the root cause, at the genetic level, has really a great potential of causing a cure or prevent the leukemia, whereas treatment of the leukemia or the problems down the road feels more like putting out fires and has proven to have limited success over the past several decades.

Our goals for gene therapy would be really to prevent catastrophic transformation to leukemia, and so a special consideration in that is that we would want to treat patients who are still relatively healthy. Therefore, the safety is of very high importance to us. The last point is that, in addition to preventing the catastrophic side effect — is also that patients need an alternative cell source for bone marrow transplant if they don't have a matching donor. That particularly affects minority and diverse patient populations. Thank you for your attention.

MS. ROWZEE: Thank you for your comments. Our next speaker is Bhisham Prithwani.

We will try our next speaker, Vedansh Singh.

Next speaker is Brajesh Singh.

I do believe we have Jenny Klein online.

MS. JENNY KLEIN: Hello. My name's Jenny Klein. I am a patient with mucolipidosis type III and a community member of the National MPS Society and no financials to disclose.

I was diagnosed with mucolipidosis at 9 years old, and throughout the course of my life, I've had nine surgeries to manage the bone and joint pain I experienced as an adolescent and as a young adult and to improve the quality of my life. At the time of my diagnosis back in the late '90s, my life's trajectory was unknown. There were very few cases reported in the United States and around the world, and even today, there are only a few hundred cases known worldwide.

For a disease like mucolipidosis, gene therapy holds great promise, and it may be the only modality that has the potential to provide therapeutic benefit and treat the underlying cause of disease; however, I caution using the word *cure*. It's certainly important to offer hope, and it's always important to develop and advance new technologies, but I think we need to make it known that several factors, including but not limited to the route of administration, capsid selection, dose, et cetetera, can all have an impact on a treatment outcome. Mucolipidosis is multisystemic, and that is the case for many rare diseases. Many of the friends I have grown up with also suffered from bone and joint pain, but many of them have lost their battle to mucolipidosis from cardiac complications.

With that being said, I feel very strongly that the patient community should be involved in the drug development life cycle very early on. As scientists and drug developers, we need to be intentional about listening to the patient community, in understanding the burden of disease from their perspective. It would be great to know one thing that they could change, one symptom they could fix, one problem that could be solved, but it's also important to look at the quality of life and how a gene therapy could improve the quality of life. And sometimes that might mean using additional interventions, such as a surgery, a small molecule, and maybe, in some instances, enzyme replacement therapy to complement the gene therapy.

When a new therapy is under investigation, the patient community also needs to be aware of what the intention of a clinical trial is and how that may differ from an approved therapy. For those who have the potential to reap significant benefits and for those who may not have another treatment option, the choice to enter a clinical trial may be a no-brainer. And I can tell you, as an affected adult patient in this community living with a progressive disease, the opportunity to access a gene therapy sheds light on what could be a potential benefit, but we also understand the benefits may not be as great as they would have been with early intervention.

So as a community, I just want to keep that in mind as we begin to look at the patient population as a whole. Thank you, and I appreciate the opportunity to be here today and speak with you all.

MS. ROWZEE: Thank you. Our next speaker is Robert Wiseman, Jr.

MR. WISEMAN: I am Robert Wiseman, Jr. I go by Bobby. I am the son of Alice Edna Childs, the oldest grandson of John Brown, Sr., and Dorothy May Brown. I'm a 51-year-old Black male diagnosed with hemophilia B, severe, that was diagnosed about 3 days after circumcision. Cleared my hep C on the Sovaldi trial. Live in Sacramento, California. I'm a same-gender-loving man that is happily divorced, the father of 22 children, because I was a foster parent for roughly 20 years. I have 16 nieces, nephews, and godchildren. Current occupation, I'm the CEO and founder of both a nonprofit and a for-profit company. Ordained deacon, and I'm a candidate for my MDiv in social justice and practical theology.

I say all of that because that goes into my experience with gene therapy. It is not just me in this journey — that being a person with hemophilia B co-infected with many things. Gene therapy is unique to and for me, which is my definition of a cure. That my experience and journey of being — and I'm going to just say it as is: the guinea pig. It was new, it was novel, and many unknown answers and questions at the same time. Trailblazing in the fact that my participation and decision to go into it was not just mine alone. It was conversation with my mother, conversation with my kids, conversation with those tight in my network. It was complicatingly uncomplicated, the amount of lab work, questionnaires, et cetera et cetera. It was worthwhile because I went from less than 1% clotting factor to now, where I'm hovering roughly 57, 60ish percent. It's representative of my journey and where I'm going off my own script? Hearing all the other voices, both the parents, those affected, what's clear to me, very clear, is that gene therapy is not a document. It's the people. It's the experiences, good and bad. It's the communication with providers, not just the main doctor, but the research coordinator, all of that. Yes, there are risks, and the benefit is quality of life that's subjective by family and person. No document can quantify what that is. That's personal experience. The question has been asked to me before, would my life have been different without the gene therapy and/or the hemophilia B? I can't answer that, but what I can answer is that because I was able to participate in a trial, I'm able to be a voice for those who have not been given access, those who have questions.

Speaking as a member of the bleeding disorders community, I offer the FDA this question, and all those: Our women with bleeding disorders have not been included in the trials. They are part of our community. If the goal of overall medicine is access, quality of life, and fairness, I pose the question. Let's have all of our communities engaged in clinical trials. That this representation of the 21, 22 people — this is quite powerful to me. That it's ironic that it was pulled together to hear the different stories, the different journeys. There's power in this that cannot come down to a statistical number, but what is evident to me is the impact of the journeys.

MS. ROWZEE: Thank you, Bobby, for your comments.

Our next speaker is Will, William Hubbert.

DR. WILLIAM HUBBERT: Thank you so much, Anne, and thank you to this entire panel for hearing me today. My name is Will Hubbert. I'm a patient advocate and a volunteer with the Hemophilia Foundation of America. I am not an employee. I mistakenly filled that out, so I just want to clarify that these are my views and my views alone. I meant that I was affiliated with the organization, not that I worked with it. That said, I do have no financial conflicts to disclose at this time.

So, like Bobby and like James before me, I am also a patient with hemophilia. Unlike both of them, I have not elected to pursue a gene therapy at this time. I want to speak about my perspective on the flip side of things, someone in the wait-and-see camp about some of the risks-benefit, cost-benefit analysis that goes on in my head and what I'd like to see as someone weighing this decision. I know that there are lots of people to speak to, and I'll keep it quick to three points.

The first point I want to make is about transparency. As James said in his remarks, he studied the therapy for a year before he felt really comfortable with the science and secure with that decision, which is an amazing amount of due diligence. Robert also spoke a great deal about that decision process and all the stakeholders and the process he went through. Hemophilia is ground zero for a major iatrogenic catastrophe in the contaminated factor episode of the '80s, so this is a community that knows full well the risks that come with some novel therapies, and that's something that certainly weighs into my decision. I applaud many of the investigators and manufacturers of therapies thus far and the transparency they've had at the trial stage. I would just say that as it extends past trials, I would like to see that transparency continued as patients come in, once that therapy does have FDA approval. There needs to be really transparent and frank acknowledgment of the uncertainties. What will your factors look like after this intervention? How long will you keep those levels? This can't be something where it's sort of salesmanship or horse trading. It needs to be really honest and straightforward so patients can make that informed decision.

The second point I want to make is that this is an irrevocable treatment or intervention, right. I'm going to live with hemophilia for the rest of my life. If I elect to take a gene therapy, I will also be living with that for the rest of my life. And so is a big leap of faith in many ways, we know that there is a lot of due diligence that goes into these trials. They look at long-term follow-up, but there are still unknowns about what happens 10, 20 years down the line, potential complications. All of these things are going through my head, and I can certainly be brought around on some of them. I'm not saying that that's an insurmountable barrier for me, but that is just something to keep in mind — that this is something patients have to consider.

And then the final point I want to make is that, as I think has been illustrated by this

group of panelists, everyone's decision is going to be different, because a gene therapy is necessarily an alternative to a different regimen of treatment, and in some cases, there is no — let alone cure. There is no treatment, and you're talking about diseases that will necessarily be fatal if left unattended. In other cases, you're talking about diseases that do have some treatment modalities available. For my part, I don't want to say that hemophilia has been easy to live with, but I feel like my disease is well-managed on a factor product, and that certainly weighs into my decision. I'm necessarily comparing the unknowns of a gene therapy against the knowns of my factor product. And so even within hemophilia, there's going to be a diversity. What's the state of your joint health look like? Do you have an inhibitor or another complication? All these things presumably weigh into the decision-making process, but then, even across diseases, it's much wider.

Patient groups and patients are going to have individual concerns and heuristics based on the state of their individual diseases.

I just want to thank you for listening to me today, and I really appreciate this opportunity to give my views on gene therapy.

MS. ROWZEE: Thanks, Will. Our next speaker is Bradley Williams.

DR. WILLIAMS: Thank you. My name is Brad Williams. I live with a type of muscular dystrophy called limb-girdle muscular dystrophy R2, or dysferlinopathy. I'm also a scientist who works for an advocacy foundation, the Jain Foundation, which is focused on this particular disease; however, I'm speaking today on my personal views and more about what I see in gene therapy in general rather than the specific situation with my disease. My type of MD is caused by a genetic mutation which causes the body to be unable to produce a protein called dysferlin, which is necessary for muscle health. Also, in the way of disclosures, I potentially stand to receive payments from Sarepta Therapeutics based on milestones from their drug development in various forms of limb-girdle muscular dystrophy.

Gene therapy is in a special category among genetic diseases, which, as we heard earlier, comprise most rare diseases. It's the only treatment modality which really goes to the root of the underlying cause with the disease, rather than just treating symptoms or downstream effects. Successful gene therapy is what patients with rare diseases have been waiting for many years. There's just not an alternative that's as promising as gene therapy for really fundamentally changing our experience with the disease. We need to make gene therapy available for as many diseases as possible as soon as possible. But from the patient perspective, developing treatments is taking a lot longer than we patients would hope, and there's only a relatively small fraction of all the rare genetic diseases out there that have active development programs in gene therapy. Gene therapy development needs to become less daunting, particularly for disease areas with small patient populations or less resources.

I want to remark on the initiatives on standardizing gene therapy development and manufacturing that Peter Marks has spoken of at recent presentations. I think that's an important thing, and I salute the FDA for looking forward to making gene therapy more amenable to more disease areas. I encourage FDA to work in partnership with both federal agencies and advocacy organizations to move this forward.

Another thing that I want to remark on is the need for patient education. We've seen in the presentations today that a lot of advocacy organizations have a very deep knowledge of all the science and all the technical issues involved in gene therapy, but that's not necessarily true for all of the patient community. In my experience, patients sometimes tend to have unrealistic expectations about benefits, risk, and the development timeline for gene therapies. I think to get better-informed opinions for feedback from the patient community as well as for patients to be able to make decisions about clinical trial participation and whether to take a gene therapy drug after it becomes available, there's a lot of work to be done. That's not purely FDA's responsibility; however, I think FDA has a role to play with partners of other federal agencies as well as the advocacy community.

To summarize, gene therapy offers a transformative approach to many rare diseases. It's critical that we take the steps to enable it to fulfill its potential. I thank FDA for organizing this event.

MS. ROWZEE: Thanks, Brad. Our next speaker is Heather Smith.

MS. SMITH: Good afternoon. I'd like to disclose I'm a paid consultant for MustangBio.

My name is Heather Smith, and I'm president and founder of SCID, Angels for Life Foundation, which I started 14 years ago. More importantly, I'm the mother of two children born with severe combined immune deficiency, or SCID. SCID is the most severe form of primary immune deficiency, and in lay terms, these babies are born without a functioning immune system, leaving them vulnerable to infections as simple as a common cold. This is what happened to my first child. Born before the era of SCID newborn screening, at the age of 6 months, he came down with what we thought was his first cold, and nearly 4 weeks later, he passed away.

In 1994, when I became pregnant for the second time with another SCID baby, we researched our options and learned the standard-of-care treatment for SCID at the time was a bone marrow transplant. We also discovered that being treated at a hospital with expertise in SCID would require us to travel out of state. We weren't crazy about that idea, but we were willing to do anything to better the health of our child. During that visit with the medical experts, we learned about an experimental treatment therapy that was successful in the animal model but had not yet been done in humans. After reviewing the research papers and many discussions with our family, we opted for the experimental treatment, and in 1995, my son, Taylor, was the first in the world to undergo a bone marrow transplant in utero while I was still

pregnant.

Taylor's led a healthy and productive life, but during the spring semester of his junior year in college, we learned his immune system was waning, and it was only a matter of time before he'd have to seek additional treatment. Again, we did our research and weighed the risks and benefits associated with each option, but when your options are limited, like they are with SCID, you must make a decision based on the potential benefits foremost. That's exactly what Taylor did when he decided to enroll in the NIH lentivector gene therapy trial. Seven months following graduation from college, Taylor was in-patient at NIH, receiving his gene-corrected cells.

As someone who has personally helped pioneer an experimental therapy and then gone on to assist her child in the decision-making process surrounding gene therapy, I think I have a pretty valid understanding and expectation of the risks and benefits surrounding gene therapy for SCID. However, when I read the consent-to-participate form — specifically, the possible late effects from gene transfer — I recall reading the paragraph where, at 2½ years after treatment, one study subject was found to have a group of blood cells with more than the intended number of copies of the corrective gene inserted in each cell, possibly indicating a higher risk of leukemia.

Now, 3 years after watching my son sign that consent form, he's been notified that clonal expansion has been seen in more of the study data, including his own results. It is my understanding that safety rules were written in the protocol prior to starting the study, and if one of those rules were triggered by a certain percentage of study participants, enrollment is stopped and the trial is suspended, which is what happened with the trial my son is in. Fortunately, there is no evidence in any of the study participants that there is an increased risk of cancer or any abnormalities in the blood and immune cell formation or function. But this past Fourth of July weekend, when the SCID Angels' private Facebook group received a post from a SCID parent saying it's been seen on the ClinicalTrials.gov website that the trial has been suspended, and the reason, in parentheses, states, "Clones representing 10% or more of the subject patients' myeloid lineage have been detected or evidence of malignancy found," you become very alarmed.

You can only imagine what it felt like to be in my shoes. How was I supposed to keep a group of nearly 900 SCID patients and family members from around the world calm when I was panicking myself? Wouldn't it be nice if, within the safety rules, something was written that if a safety rule is triggered, immediate notification to enrolled study participants is made surrounding the circumstances before updating the ClinicalTrials.gov website? What a difference a policy like that could have made to our SCID community.

Lastly, before I end, I must mention the kiddos seen in my slide represent a small fraction of the 26 ADA SCID patients who are currently on a waiting list to receive

gene therapy because they don't have a matched sibling donor. The idea of companies investing in gene therapy treatment in hopes of making a profit isn't working. The lives of these pictured here are just a few of the patients who are counting on us to solve this. These lives need to matter too. Thank you for your time.

MS. ROWZEE: Thank you, Heather.

Our last speaker is Ryan Hallock.

MR. RYAN HALLOCK: Hello, everybody. My name is Ryan Hallock. I am here on behalf of the National Hemophilia Organization. I'm not receiving any compensation for myself. I am somebody who has received gene therapy for the treatment of hemophilia B. Prior to my gene therapy, I was very much just somebody who was living with hemophilia. That included multiple infusions a week and spontaneous bleeding with no known source. This led to issues with a life of just going to work, family, friends, you name it. Hemophilia did impact my life, one I always had on my mind. Now for —some — I believe we have quite a few people with hemophilia on this panel today. They understand that there's complications, and I believe you have even posted a slide which talked about what was his life with hemophilia.

I received my gene therapy back in 2015. It was just a onetime infusion. Since then, my life has changed dramatically. It's been 7 years but not until this year that I have to receive any factors to stop a bleed, going on 7 years without requiring any factor. Prior to my one incident this year, hemophilia was on my mind, but it wasn't the controlling factor that it used to be. When I go places, I would sometimes forget my factor, because hemophilia is a part of me, but it wasn't always me. And then that's not the cases for others that are here on this panel — that disorders and diseases — they affect all of us every day.

For myself, gene therapy works, and I'm happy that it works, but for the study itself, it wasn't such a quick decision, like, "Oh, here we go, we've got a cure," because it's not. If you ask me, that's not hemophilia. I still treat myself like I have hemophilia, I see my hematologist like I have hemophilia. That part hasn't changed. Some of the risks and benefits that I discovered during my study is that they — there were some unknowns, there were a lot of unknowns, but as a patient, I had to be the one asking the questions. The study and the physician providing the information on the study to which they felt would be concerning. But for myself, I had to speak up. I had to do a lot of my own research, which should be the goal for every patient. I wouldn't want anybody taken into a gene therapy or making a decision without doing the research or having the answers. But now, that doesn't guarantee that all the answers will be there.

One of the questions I had was, "How long will this last?" And when I learned that we don't know, I was the one who accepted that responsibility. I know that, and I'm happy with that. And so with this study, if there's something that I can wish there

was more on was, essentially, tools that can be utilized to capture information or actively be a little more transparent, because it's a study, there are a lot of delays, and I can only see the results for myself. But for others and then maybe other studies, if we had ways that the information could be published sooner so we could see how studies are going, whether we really know how responses work — whatever it is, that tool should be accessible.

One of my key factors that I took away from that I realize, for myself, it was easier to make myself available for this study, but I believe Robert said it best: We have to make sure it's inclusive to everyone. For myself, I was in a position where I could make appointments, I could be available for the follow-up appointments, but that may not be the case for others, and so gene therapy or even a study may not be an option for them. I just want to make sure that when we do produce these studies, that we're listening to what the results are and that when we offer this treatment option, we're being inclusive.

Thank you for listening.

MS. ROWZEE: Thank you, Ryan. I think we have a few minutes left in our session, we are going to circle back and try to get back in touch with some folks that we missed on the first time around. I believe Suzette James may be on the line.

MS. SUZETTE JAMES: Good afternoon, everyone. Thank you so much for the opportunity to speak today. I have no conflicts of interest, financial or otherwise. My name is Suzette James, and I have four children, two of whom are living with CLN2 late-onset or atypical Batten disease. My daughter, Maya, age 19, was diagnosed at 9, and Xavier, age 15, diagnosed at 8. Maya has now been living with Batten for half of her life. For those that are not familiar, CLN2 is a progressive neurodegenerative disease that affects children. Most children develop typically from birth, meeting their milestones until death, usually between 6 to 12 years of age.

Our CLN2 community lives in a continual and never-ending pandemic. One hundred percent of our population dies a torturous death, and there is no chance for survival for our children, only a death sentence. We do understand the risks and benefits of gene therapy. We realize it is not a cure. We understand dosing challenges, we understand the potential toxicity issues, but the biggest risk that we and our children face is the risk of doing nothing. That risk is 100% fatal — a slow, excruciatingly painful death — a long goodbye if you will, full of uncontrollable seizures that rattle their brain, muscles twisting and contorting and spasming, blood-curdling screams and cries as the disease makes its gains.

Our children lose their vision and go blind. This terrifies them as the world turns dark, and as they try to process what is going on, they panic and are inconsolable. Gouging at their eyes and repeatedly hitting their heads with their tiny fists, they choke on their own food and on their own spit, and bit by bit, their bodies shut down. Batten disease doesn't just stop with the child, though. It has a far-reaching

and rippling effect on anyone in its wake. One parent told me the story of her child after being put on hospice. The family huddled around and was close by as they decided to begin the process of letting her go. The mom had prepared herself and knew what to expect. She knew she would have to make the hard decisions, but the dad sat watch over his little girl, and even though he agreed on their plan initially, he begged that they give her water. "She is thirsty," he cried and pleaded; "Please, please give her some water." The mom, taken aback by her husband's reaction, eventually gave in. She hadn't ever seen her husband in this state, and as soon as they gave the girl water, her body immediately rejected it. Her body heaved and convulsed, and she vomited up blood. She left this world days later.

That was 4 years ago, and the father is just now starting to come back to himself. He is just now beginning to generate some income again. Gradually, he is finding his new normal. CLN2 and all Batten disease destroys everyone in and around its path. There are far too many of these similar stories where families and loved ones have been torn apart emotionally and financially — parents, caregivers, siblings, grandparents, and teachers. You are never the same after Batten. And those numbers and lives lost need to be calculated in the population, too. This community is tired of hearing that at least the numbers of children affected with CLN2 are small. We hear all sorts of reasons why research and treatments aren't being funded or given approvals. CLN2 is a critical, critical public health issue, and it deserves the same level of commitment as any other pandemic.

As I stated to the FDA in March, and as stated by the FDA themselves, time is of the essence. We have to keep the needle moving forward. We need a pipeline for a lifeline, and gene therapy is part of that pipeline. So you ask us if we, as parents, understand the risks of gene therapy; we do. But can I challenge you to entertain another question: Does the FDA understand the risk and ethics of not doing anything? And by doing nothing, we are ultimately sentencing these children to death. And when we weigh one against the other, the risk of not doing gene therapy far exceeds the risk of administering it. Thank you for your time.

MS. ROWZEE: Thank you, Suzette. I'm going to do a quick roll call for speakers we missed initially. Luke Rosen? Robert Rydberg? Bhisham Prithwani? Vedansh Singh? Brajesh Singh?

Thank you again, everyone. We'll now open it up to our FDA panel. I think they have some questions. Folks from the FDA, please feel free to begin questions.

DR. ELIZABETH HART: Good afternoon. My name is Elizabeth Hart, and I'm one of the branch chiefs within OTAT. I'd like to begin by thanking each of you for sharing your stories. Each patient's voice matters a lot to us. My question is for those of you who are representing organizations; I've heard that some of you had conducted some qualitative and quantitative studies to get perspectives from your disease community. Given that many rare diseases are heterogeneous, how have you worked

to include patients and families who have different experiences to ensure that you hear from the total patient community and hear the varied patient perspectives?

MS. ROSENBERG: As I explained with our study, this was really important to our community, because the disease is so different for each person, and so our focus group specifically targeted different types, both age, types of disease, location, caregivers versus patients, to really try to understand the full totality of disease and the natural history. And then in addition, so based on those focus groups, our survey then took into account the varying different types of disease, recognizing any survey or focus group is going to have limitations because of who's going to answer it, right, so already, you have to have someone who has a computer and that has access to internet. You're certainly losing that population, and we absolutely understand that. But we're hoping, by having those different targets — caregivers, patients, neurological and non-neurological — that we're trying to capture the biggest population as possible.

DR. ALLYSON BERENT: We really tried to balance that with the demographic of the different genotypes that were represented in a natural history study that we have of over 500 individuals and a global Angelman registry that we have of over 2,000 individuals. Actually, our focus group completely, perfectly represented the demographic of the genotypes, and really, the phenotype/genotype correlation in Angelman syndrome is pretty significant. With that said, if we think about the heterogeneous nature of this neurodevelopmental disorder, it's all very severe. And so the level of severity is pretty minimal as it compares to neurotypical individuals, and so some individuals may not have an issue, let's just say, with sleep but have a significant issue with motor dysfunction.

All individuals are nonverbal. All individuals have a seizure disorder, some a little bit worse than others. So the heterogeneity really matters when we think about small changes. It doesn't actually play a huge role when we think about large changes. And so we did try to represent all ages, because I think that's also important; the risk that a 25-year-old patient and family is willing to take versus a 2-year-old patient and family is willing to take is quite different, especially where people get used to the idea of what they have versus the idea of what they want. And I think that does change over time, and we really talked a lot about that.

We also did a survey of over 300 people, and it was equally represented amongst genotype and age. And so I think our answers were quite representative of the population and overall the severity of the disease is severe regardless of age or genotype. It's just more a matter of the risk families are willing to take in terms of waiting for their turn, understanding if they have to give a different dose level for gene therapy. Individuals may not want to be on a low dose, high dose, or middle dose, and they may want to wait for the best dose, which may be determined in a Phase 3 trial, versus individuals that will not enroll in a sham or placebo-controlled study, which is the majority of them, frankly.

My worry, and I think the worry across all genotypes, was that the idea of enrolling the Phase 1/2, because people don't want to be in a sham or placebo control, or if there's not one in the Phase 1/2 and only in that Phase 3, or again, individuals feel that that's unethical and that they don't want to put their child through that. That is where, overall, regardless of the representation of heterogeneity, it was very similar in risk/benefit, and they all have the same desire for this new type of benefit. It just might be marginal.

MS. HARS: I just wanted to add a comment that it's difficult to reach the people we can't reach, by definition, who may be on different socioeconomic challenges or just not connected to the Internet world to the same extent as more affluent people, but we can make the assumption that for diseases that need — where the gene therapy would be delivered, sort of like a bone marrow transplant — that patients of color or in other diverse groups are at a disadvantage with the classic treatment of unrelated donors. They have a much harder time finding matches. So gene therapy, in that sense, would really address their needs specifically or more so than other treatments and therefore would be more equitable in a way, even though they may not have a voice to speak up, so we are here to speak up for them.

DR. KIM STEPHENS: We have a unique opportunity within the Hunter syndrome community because we do have two clinical trials open that are sort of ERT that crosses the blood-brain barrier and gene therapy. We're having this, what people are choosing. We're seeing folks that are further along in the disease choosing gene therapy because there isn't an alternative for them; they don't have that ability to go into another clinical trial. So we have that urgency, and we see this a lot with some of our older folks that aren't necessarily going to be in a pivotal trial. And we need it now, because these kids are also getting to the age where they typically pass, at age 14 and 15.

DR. WILLIAMS: I was just going to mention about — on the issue of patients being unwilling to enroll in a trial where if they're afraid they might end up in the placebo group and not have any treatment, what I've seen done in some gene therapy trials in muscular dystrophy is that there will be initially a placebo group, but then later on in the trial, those in the placebo group actually get treated, so everyone eventually gets treated, just at different points in time. I thought I would throw that out there and, you know, see. To me, it seems like a reasonable approach if you need a placebo group. I would just ask what other people's opinions are on that.

MR. TUSHAR TANGSALI: Under the prospect to Brad's comment, the issue with gene therapy and the placebo arm, as I see it, is that typically, the gene therapy, at least in the Duchenne muscular dystrophy domain, goes on for 48 weeks, which is a year. In DMD, the trials are organized with 2:1 or 50:50, where 2 out of 3 patients get an active drug and 1 gets placebo. The first issue is, we have a considerable natural history domain of information on the last 10, 15, 20, and 30 years, so I don't know what difference we are expecting from the placebo, from the comparison to the

placebo arm.

The second issue I see is that most of these gene therapies are administered using AAV virus, AAV-9, AAV-74, AAV-8, any of those AAV things. Now what happens is, a kid may enter the placebo arm. He is checked for antibodies, he has none, but he enters the placebo arm. A year later, when he is going to get the active drug, another potential issue is, a year from now, he could be exposed to some virus, say a common cold virus, and he could have antibodies then. How do we address that? So the kid essentially wasted a year on placebo for a trial that he is eventually not even going to get.

MR. WISEMAN: I'm loving this rich conversation, and I'm going to echo this point. Step formulas work with a pill you can take. Life is not a step formula, nor placebo nor non-placebo. Life is not measured or cannot be measured by "let's try this for an extended period of time." The value of the individual and the individual in the family that's taken care of him or her cannot continue this up-and-down roller coaster of wondering and waiting for what could be, when the powers that be, I personally feel, can work together — government and communities and medical facilities — to maintain hope, take away the heartache that is there when a parent has to be in that moment of decision or the young person who transitions to young adult and adult, where they're empowered because of what has been poured into them. I strongly urge folks to move away from a black-and-white bottom line of statistics — I'm very clear on this — and to hear the human voice and impact. It may not be fiscally sound, but it is correct, just, right, and honest.

MS. ROWZEE: I want to thank everyone again, all of our Session 1 speakers, for joining us today, for your time, for sharing your personal stories, for this rich conversation as well. I know that there are some folks who I couldn't get to first on the comments screen; again, we'll show the information again at the end of today's meeting, but please place your comments in the docket. There's some rich conversation going on in the chat as well. Folks, if you have thoughts to share that aren't voiced today online, please share them in the docket. We're going to do a quick break. We're due to be back at 2:05 Eastern Time; we'll move into Session 2 then. Thank you again, everyone.

[Break 01:59:25]

MS. ROWZEE: Good afternoon, everyone. Welcome back from the break. Once again, thanks to everyone for joining us today for our Patient-Focused Drug Development Listening Meeting on Gene Therapies. We'll now move to the second topic of the meeting, patient and caregiver involvement in clinical study design and execution.

We have 13 speakers for this session. Each speaker will have 4 minutes. I'd like to remind our speakers again to please stay online after you speak and for the duration of the session so that FDA panelists can ask questions at the end of the session.

Our first speaker is Corrin Jackson.

MS. JACKSON: Hello. My name is Corrin Jackson. My daughter, Evelyn, is currently 6½ years old. She was diagnosed with CLN2 Batten disease in October of 2019. I'm speaking today on behalf of the CLN2 Batten community to present some of our thoughts on the patient involvement in clinical design and execution. I have no financials to disclose.

On November 15, 3 years ago today, just 3½ years old, Evelyn was being sedated for major brain surgery to install a device that allows her to receive an enzyme infusion. It was our hope to slow down the progression of her disease, with the promise that gene therapy would soon be available. Now, 3 years later, my daughter continues to regress, to lose her abilities to function in life, while we wait for gene therapy to be available, despite many reassurances that they are very close to starting trials. When considering clinical trial design and execution, myself as a parent, and our community at large, values being offered the opportunity to identify what is both important and meaningful to us. It is important we collaborate with the scientists and drug development teams in identifying what specific endpoints and assessments cases may be evaluating.

Part of family collaboration with drug development companies begins with a patient advocate assigned to help the communities to questions. In our family's experiences, we have to use the Contact Us email link on the biotech company's website, receiving a generic email back. Family emails are never followed up, and they are never connected with an actual person at the biotech company. Hence, collaboration is missed.

In designing execution, biotech companies have sent the National BDSRA Foundation surveys to share with the Batten community, survey questions asking the community feedback. What was our hopes with gene therapy? Our expectations? Our worries? Our hope is to allow our child to live a somewhat normal life, because time is of the essence; the sky is falling; our children do not have the luxury to wait. We want accelerated approval processes, realistic eligibility criteria, a design taking into account existing approved therapies, and efforts to ensure trial continuation in today's market.

There is a lack of input and collaboration when designing trial eligibility criteria. Bio companies set an unrealistic criteria that a late infantile disease cannot actually meet, because most hallmark symptoms of Batten disease immediately deny a child eligibility to a trial. If a criteria is so stringent that no patients can ever enroll, defeating the purpose of testing safety. A survey was shared with the CLN2 community, in it asking a very important question, reworded many variations, questioning whether families would stop one treatment to trial a gene therapy.

But results for this question and major craft and designing trial execution have never been discussed with the CLN2 community. Patient perspective is disregarded

when a clinical trial is stalled indefinitely, which is a death sentence for a child, who are continually led to believe it was so close. How can the FDA ensure a child commences on human studies once given the green light to start? We have seen a lack of patient and family involvement, when FDA reviews preclinical results with a biotech company. I have asked and suggested that the biotech company include a family presence during the IND meetings with the FDA to give perspective, only to be denied. A community perspective to what truly mattered to the patient; what benefit/risk tradeoffs in therapeutic areas would have been crucial, when a preclinical study that has satisfactory animal model data is submitted for IND application review with the FDA? It would have been dire to hear feedback from a patient and caregiver when the FDA requests larger dog animal models study, sending the biotech company back to the start for another 2 years. Patients need consistency, a standardized, FDA-approved document of requirements for all biotech companies to adhere to when completing any preclinical study involving animal models, so that we may need humanely test on the least amount.

Patients have a right to understand why a trial is put on hold. The FDA and biotech companies need to be transparent, because our children do not have years to ponder and wait. Clinical trials are intended to benefit the patient with a rare disease. Therefore, enhancing the incorporation of the patient's voice in drug development throughout the whole design execution process is critical to ensuring gene therapy for an unmet need has accelerated approvals while measuring safety. Thank you for your opportunity to present and consider the patient involvement in clinical design and execution.

MS. ROWZEE: Thank you, Corrin. Our next speaker is Julia Taravella.

MS. TARAVELLA: Thank you. Hello, everybody. I want to talk, kind of continue the talk that the previous speaker mentioned. And I want to actually bring a bigger focus on their, patients' development, patients' involvement in their rare diseases' developments for gene therapy and ultra-rare diseases, and very big difference with those.

The disease I'm representing is called aspartylglucosaminuria. I put the dots there. It's a pretty big word. In short, it is AGU. It is the neurodevelopmental, neurodegenerative disorder, one of the lysosomal storage disorders, pretty similar to Batten.

This particular disorder is less severe to progress. And the premature death originally in published literature states between 25 to 30 years of age, and now with the better health care and better life quality, it actually extends to 45 years of age. Because of that, the disease is a lot less severe. It takes a long, long time to diagnosis.

My oldest son — I have two sons with the disease — my oldest son was diagnosed whenever he was 18 years old. And I remember him having the test for this

particular disease whenever he was 12. And the results actually came back false, negative, but the sample is contaminated. And I asked the doctor, "Can we resend the sample?" Which, at that time, the doctor gave me a very interesting answer that I think stuck all my life with me. He said, "You really don't want your child to have a lysosomal storage disorder, because those disorders has no treatment." So, it is one of the simple disorders, meaning monogenic disorder in gene replacement therapy showing promising approach for the treatment and possible cure. But it is an ultra-rare disease, meaning that the patients, the amount of patients around the world is somewhere between 200 to 300.

What happens with the ultra-rare diseases is, there is no biotech; there is no pharmaceutical companies. There is actually no grant; nothing exist. When one of my children got diagnosis, we started the research. And soon after that, we realized the amount of money that needed, so we started the foundation. I couldn't call it Aspartylglucosaminuria Cure, so we called it Rare Trait Hope Fund. We actually raised money and funded all of the developments up to pre-IND that was held in 2018 with FDA.

The pharmaceutical company was interested in it, worked on it little bit for a few years, but then actually dropped the indication, because it is noncommercial indication. So we actually restarted it, and we decided to go ahead and start the clinical trials and fund it completely. It is a very, very difficult venture — very, very difficult event to hold for the small community of the parents. So where we are now, we actually produce the medicine, and we're actually starting the toxicology study — hopefully start the clinical trials within the next 6 months to a year.

With that, I want to make a point that there is a patient community. Involvement is big when the pharmaceutical companies are actually making an effort to bring those diseases to gene therapy developments. The community have to make the sacrifices and actually do the work by themselves to fund 100% the developments when the disease is ultra-rare and there was no funding available anywhere. Thank you. That's the point I want to make.

MS. ROWZEE: Thank you, Julia. Our next speaker is Kathryn Bryant Knudson from The Speak Foundation.

MS. KATHRYN BRYANT KNUDSON: Thank you so much for allowing us to be here today. My name's Kathryn Bryant Knudson, founder of The Speak Foundation. I also live with limb-girdle muscular dystrophy type 2I.

Right now, we're at a vital time for limb-girdle muscular dystrophy. As a patient and the founder of an advocacy organization focused on limb-girdle muscular dystrophy, I work firsthand with patients from every subtype of LGMD. For the past 15 years, I have looked and looked and been at the forefront of this landscape looking for any shred of hope.

There are currently no treatments on the market for any form of LGMD. However, we are seeing potential first-time gene therapy products specifically for the forms 2A, 2B, 2C, 2D, 2E, 2I, and 2L. Other companies are creating additional treatment modalities, such as substrate supplementation, which could complement and provide a more powerful combination approach to treatment. And further, even more companies are doing potential treatments as well. And disclosures, we do have sponsorships for our events, such as the International LGMD Conference and our recent externally led PFTD from Sarepta, ML Bio, Edgewise, Vita, and AskBio.

I want to share that patients, more than anything, want to see their disease progression halted. Preserving muscle tissue that is left would be a win for us. Seeing the missing protein expressed in clinical trial biopsies makes us willing to take risks to see potential treatments.

However, we do have drug development challenges for the LGMDs. First, this is an ultra-rare disease with many subtypes. It makes traditional randomized trials with placebo controls almost impossible. Patient recruitment is also very difficult, due to small sample sizes in many of our subtypes, and locating patients who meet necessary inclusion criteria is very challenging.

The heterogeneity of LGMD is very obvious when you start to encounter many of the patients. I've seen hundreds of patients living with different and various forms of LGMD. I am always amazed at the variability in any particular subtype. You can see the loss of ambulation at age 8 and then at age 16 within the same subtype. Even siblings with the same genotype are often progressing at various rates of speed. Then we also have a very slowly progressing disease in many of the subtypes. It's hard to rely on functional outcome measures, because it would take years to show improvement. If you looked at a measure like walking or ambulation, the variability between patients will mask a treatment effect.

There are possible solutions for LGMD with clinical trial designs. First, we can adopt natural history studies as external controls for trials and use more innovative designs. We have lots of natural history data for many subtypes of LGMD. In fact, there are two now that have gone on for 12 to 15 years in many subtypes. Use surrogate endpoints and biomarkers, such as protein expression in biopsies, for accelerated approval versus waiting on functional outcome measures to show benefit.

We can incorporate more patient-reported outcome measures with emphasis on what is important to patients, such as breathing issues. Patients are so concerned with their ability to breathe and feel strongly this outcome measure is sometimes ignored. We'd also like to see more platform approaches for subtypes that are within the same protein complex. It takes too long to approach gene therapy one subtype at a time. We want to see the recruitment of more progress in nonambulatory patients in trials. We deserve the right to try, and the risk is ours to take.

Last, we think a neutral advocate not associated with industry should advise patients on the future implications of gene therapy, since this is not a treatment that will wash out of the system. Patients need ongoing medical guidance in future years to address complex issues of gene therapy. Thank you, FDA, for allowing me to speak today.

MS. ROWZEE: Thank you, Kathryn. Our next speaker is Kim Nye.

MS. KIM NYE: Hi, my name is Kim Nye, and I am the founder of TESS Research Foundation for SLC13A5 Epilepsy. A big thank-you to the FDA for inviting me to share our story here today.

Like so many in the rare disease space, I started our organization because my family is directly affected by a rare disease. When our daughter Tessa was born in 2003, we thought we were having a healthy baby. But Tessa began having seizures shortly after birth. We saw her diagnosis shift from benign idiopathic neonatal seizures to catastrophic epilepsy. Medications, surgeries, diets, clinical trials, and research all failed Tessa for more than a decade. She was having hundreds of seizures a day, but we had no idea why.

In 2013, our world came crashing down when I gave birth to our fourth child, a baby boy who we named Colton. He seemed healthy, but just like his big sister, Colton began having seizures shortly after birth. He was only hours old, but I knew my son would never talk or dress himself. Colton's birth made the medical puzzle a little bit easier. A researcher was able to find a genetic marker for the disease, SLC13A5 citrate transporter disorder.

But was the diagnosis the finish line or the beginning of a new race toward a cure? Our neurologist, Brenda Porter, agreed that diagnosis should not be the end of the journey and that we should use this genetic knowledge and translate it into better treatment options. In 2015, we started TESS Research Foundation, and in 2017, I put my whole family on a plane and we flew to the University of North Carolina to meet with academic researchers to ask if they would create a gene therapy for SLC13A5 deficiency. They said yes, and our organization began funding the preclinical development. In 2020, the project had been de-risked enough for an industry partner to step in and add it to their pipeline. There have definitely been some ups and downs in the biopharma space, but we are still hopeful that with the help of regulators, we will move it into clinical trials in the near future.

So why are patients and caregivers so important, especially in newly discovered, devastating, ultra-rare diseases? The simple answer is that patients and caregivers are the experts in the disease. They are the ones living this day in and day out. This lived experience of the disease becomes very important in clinical trial design and execution. Families know the complexities of this disease because of their lived experience. The life-threatening seizures that begin shortly after birth that are hard to stop even with seizure medications, the frustration of being trapped in a body

unable to speak, and the debilitating movement disorder that affects daily life. Many of our families have two or even three affected children.

Because SLC13A5 epilepsy was a newly discovered disorder, this is what the landscape looked like when we started. It was a bunch of zeros and nos. There were fewer than 10 kids diagnosed and no funding or toolkit in place to accelerate the development of treatments.

We have made measurable progress since 2015. Here is what the research landscape for our disease looks like today. There are no more zeroes and far fewer nos. We have millions of dollars going into research. We have a patient registry and natural history study. We have a gene therapy in development.

On the one hand, it is amazing that we have a treatment in development. On the other hand, we only have one. What happens if this drug never makes it to market? What happens if this gene therapy doesn't work? How do we create more shots on goal? How do we make sure that data silos don't undermine drug development and fail the patients who so desperately need a treatment?

I don't think a family like mine could go from disease discovery to potential disease-modifying treatments in a few years without the passion and urgency of the patient voice. I believe that patients and caregivers deserve to be a part of the conversation from the beginning of a gene therapy development. It takes a collaborative team of patients, advocates, clinicians, researchers, and industry partners in order to turn the patient experience into a protocol that has meaningful endpoints. It is the patient voice that helps foster precompetitive data sharing in our scientific convenings. This data sharing results in better science and a better drug. If we are going to ask for families to participate in gene therapy trials that have potential high risks and high rewards, then we need to empower families to participate in the development of these treatments.

I want to close by thanking my family, pictured here, and all the families in our SLC13A5 community. Thanks so much.

MS. ROWZEE: Thanks, Kim. Our next speaker is Johann Mentz.

MR. JOHANN MENTZ: Good morning, or good afternoon, everyone. My name is Johann Mentz, and I'm the founder and president of the WWOX Foundation. And I don't have any financial disclosures to make. We can move to the next slide.

And I'm also the parent of a little 5-year-old girl named Lucia, who suffers from a devastating disease called WOREE syndrome. And I'm going to tell you a little bit more about that. But first and foremost, thank you to the FDA for the opportunity to say a few words today.

You can see some pictures of Lucia there. It's been a very difficult journey for us of her 5-year life battling WOREE syndrome. And if we can go to the next slide, I can

just tell you a little bit more about WOREE syndrome, which results from mutation of the *WWOX* gene.

Children affected by WOREE syndrome suffer from refractory epilepsy, profound global delay, and severe cognitive impairment. Most children with WOREE syndrome will not live through to adulthood, with average life expectancy of only 4 years. It's an emerging syndrome with an increasing number of children diagnosed each year as a result of improved diagnostic yields. Unfortunately, there's a high unmet need in terms of therapeutic interventions, which may be effective in treating the underlying genetic cause of the disease, and all conventional treatments such as anticonvulsants remain largely ineffectual.

Since Lucia's diagnosis and the founding of the *WWOX* Foundation a few years ago, we have tirelessly worked towards raising awareness of the disease, and through the tremendous efforts of the small but highly motivated group of *WWOX* parents across the world, we've raised funds to support research aiming to better understand and, more importantly, cure the disease.

During the past few years, some outstanding preclinical study results have made it clear that gene therapy holds the greatest promise to improve the outcome of our children and, at the very least, to significantly improve the quality of their life. We have helped one sponsor company working towards an IND for gene therapy by providing insights on patient experience. And this prospect has filled me and all other *WWOX* parents around the globe with hope.

I just want to talk a little bit about risk acceptance and also the design and approval concerns I have with any clinical trials. While I respect the FDA's conservative approach towards risk and efficacy, I'm concerned that the traditional models may not be appropriate when it comes to novel interventions, such as gene therapy, and the requirements of ultra-rare conditions. More specifically, I'm worried about the potential requirement for placebo and sham arms to clinical trials and equally worried about the fidelity applied to the outcome measures. As we are such a small cohort of *WWOX* parents with children facing such horrible outcomes, the prospect of participating in a double-blinded placebo or sham-controlled trial is unthinkable.

Considering the potential administration route for gene therapy treatments, targeting the brain may actually include a hole in the skull of the child. Recruitment of children to such a trial would be near impossible. Even if parents are successfully recruited for such a study, subjecting already fragile children to such an invasive procedure to only receive a placebo would completely undermine the risk/benefit equation. Furthermore, subjecting a child who may indeed be saved by potentially effective treatment to a sham may rob them of their only chance. They will most likely succumb to the disease before the study is unblinded and they can go on to the active drug.

One thing our children don't have on their side is time. And I fear there will not be a second chance to participate in a trial in the future, as a child would not survive until such time. I'm equally worried that a gene therapy clinical trial may result in marked improvements in our children and their quality of life but that these improvements may not be deemed significant enough by the FDA.

I'm therefore advocating for measurement scale that is appropriately tuned for such severe conditions as WOREE syndrome. While certain outcomes such as reduction in seizure frequency can indeed provide a fair and easy measure of success, a disease such as WOREE syndrome encompasses so many other aspects, which should be gauged for success. For instance, improvements in cognition or motor skills maybe require a more fine-grained measurement scale, considering the very low baseline at the start of the treatment.

Some of these improvements may only become apparent after a period of time. Consultation with caregivers and parents to develop the outcome measures is crucial. While it is important to guard against subjectivity, it is an inescapable fact that caregivers and parents know their children better than anyone.

Caring for a child affected by WOREE syndrome is very tough and takes its toll on us as careers and parents, and day-to-day care is very difficult, and seeing our children suffer countless seizures each day and ravaged by comorbidities is heartbreaking. In our case, Lucia has had close to 50 hospital admissions in her short life, with a number of them spent intubated in ICU. The prospect of a gene therapy for WWOX has provided us parents with renewed hope for the future and has helped us to get through the darkest of days. We are all taking exceptional steps to do all we can to keep our children alive for long enough to potentially participate in a clinical trial and hopefully benefit from a successful treatment.

MR. MENTZ: Despite all the suffering, Lucia is a loving and sweet little girl who has a tremendous warrior spirit, and she expresses so much joy and happiness in her own subtle way and deserves a chance to experience a far better life. I implore the FDA to really work with us — parents, pharmaceutical companies — in developing these treatments to make the journey to clinical trial as frictionless, fair, and quick as possible. Thank you for your time, and sorry for going over time.

MS. ROWZEE: Thank you for your comments. Our next speaker is Cristina Rosa.

MS. CRISTINA ROSA: Hello, my name is Cristina Rosa, and I'm very grateful for the opportunity to talk with FDA today. I speak on behalf of Juju and Friends CLN2 Warrior Foundation. When my son Juju was diagnosed with CLN2 Batten disease in 2021, my organization was established. I was motivated to become an advocate and learn more about the safety and effectiveness of gene therapy. And cell and gene treatments must be known and understood and accepted as having risks and advantages. Knowledge requirements and existing sources of information must be considered. It's crucial that the general public and patients be aware of these

medicines and also comprehend the problem that's involved and can be able to participate in discussion as possible donors or future recipients.

The necessity for effective patient and public education on the different components of cell and gene treatments is highly reviewed in this article. There is a need for high-caliber research on the views and experiences of patients and the general public about cell and gene therapy. The acceptance of utilization of these medicines is also heavily influenced by public and patient views, as well as clinical and financial efficacy data. And patients need faster and more innovative research and can contribute significantly to clinical trials that are designed to truly meet their unmet needs and priorities. If they are involved as partners in the research process at an early stage, this would be very beneficial. However, patient involvement in clinical trials regularly takes place too late in the research process, if at all.

Hence, clinical trials are often solely focused on solving clinically relevant challenges and meeting endpoints. They should focus on addressing the priorities, preferences, and needs of those whose lives are on the line or have a compromised quality of life through symptom or therapy burden. If patients are included as partners in the research process at an early stage, they can make a substantial contribution to clinical trials that are created to properly satisfy their unmet needs and goals. Patients demand speedier and more inventive research.

Patient participation in clinical trials occurs too late in the research cycle. As a result, achieving objectives and resolving clinically pertinent problems are frequently the only priorities in clinical studies. The primary goal should concentrate on meeting the priorities, the tastes, and requirements of persons whose lives are in danger or whose quality of life has been negatively impacted by symptom or therapeutic load. The effects of a sickness and its treatment, both immediate and long-term, must be taken into account.

When trial results are analyzed, sometimes it's too late, as stated before. And this journey is not easy to understand unless you have compassion and understanding. This is a battle that we all face together. Once again, thank you for your time, FDA, today on behalf of the whole rare disease community.

MS. ROWZEE: Thank you, Cristina. Our next speaker is Rachel DeConti.

MS. DECONTI: Hello. First, I would like to thank you all at the FDA for this opportunity. I volunteer for a few LGMD foundations, including the LGMD2D Foundation and The Speak Foundation. But today, I'm here to share my family's story. I also have no financial disclosures. My name is Rachel DeConti. But to my 6-year-old son living with limb-girdle muscular dystrophy type 2D/R3, I am mom. My son Jacob is amazing. He is kind, funny, sweet, smart, and adventurous. He loves to learn, is a great student, and was awarded Student of the Month last month, the first month he was ever eligible.

We learned of Jacob's diagnosis last fall after he suffered a case of rhabdomyolysis. His CK was very high, and we were in the hospital for 3 days so he could be on IV hydration. As a parent, those were the longest, scariest days, and his ultimate LGMD diagnosis was terrifying, heartbreakin, and blindsiding. After that event, one of his doctors suggested that he drink at least 48 ounces of water a day due to his nonstop activity, and he has ever since. That is a lot more than most adults drink in a day.

Jacob is always on the go. He loves to run, climbs on whatever he can, and barely sits still. With this constant activity, his legs begin to hurt after a while, and we need to remind him to slow down and stop running. It's a constant battle of letting a 6-year-old boy be a 6-year-old boy and having him rest because we know his body needs a break. Jacob's current main restriction is from playing team sports, not because he can't physically, but because of the potential strain on his muscles if he's pushed too much. He does normal activity at school and does not need physical therapy at this time.

As years pass, and the longer it takes for treatment options like gene therapy to be available to us, I can see how we may treat his symptoms differently. Gene therapy could drastically change Jacob's future. It would help significantly slow down or stop the progression of the disease to maintain or help build the muscle strength that he has now, by giving his entire body the alpha-sarcoglycan protein that it's missing. We want to prevent him from having trouble walking, becoming nonambulatory, or even worse, having the disease progress to severe cardiac or pulmonary issues.

An effective gene therapy treatment would help prevent some of the worst LGMD symptoms for my son. We would learn about and become involved in whatever treatment we could if it were available. Our prayer is that someday soon, we will be able to have multiple treatment options for LGMD2D patients, like there are for other rare diseases. We need them, and we are eager and open to help however we can.

Unfortunately, there are no trials or commercial therapies available for us to participate in today. And it isn't clear why. After years of research and trials by dedicated doctors and researchers, there is still not an approved treatment my son can have to change the outcome of his disease. Our community hears about clinical trials seeking approval to commercialize and become widespread for other forms of muscular dystrophy. LGMD is just as important and critical as these diseases. Patients like Jacob deserve to have the same focus. Fully understanding the treatment would be critical for us. Knowing the process, how it would affect him, potential side effects, and what the risks are would be among the top questions.

A placebo or dose-ranging trial could be considered. But we'd ask that at the end, all patients would get the full treatment. It would also be ideal to have multiple

forms of treatment or solutions reversing immunity to AAV to become available so he would be re-dosed, if needed, in the years to come. At 6 years old, Jacob has a long and beautiful life to live. We have heard from his doctors that now is the optimal time for him to get a gene therapy. And he would be a great candidate because of his current strength.

As each day without a treatment passes, that could change. We ask for a safe yet faster process. We want Jacob to be able to live his life to the fullest without physical and mental pain from a disease where we know gene therapy is possible. Thank you very much again for your time today.

MS. ROWZEE: Thank you, Rachel. Our next speaker is Sarita Edwards.

MS. SARITA EDWARDS: Thank you so much. Hello, everyone. My name is Sarita Edwards. I am the CEO and president at The E.WE Foundation. We facilitate resources and support for families living with Edwards syndrome, or trisomy 18, and other rare diseases. I'm also a parent advocate. Our son Elijah was diagnosed in utero with full trisomy 18. I do not have any financial interests or other relationships to disclose. Today I want to talk briefly about patient and caregiver involvement in clinical study design and execution.

Edwards syndrome is one of more than 10,000 rare diseases that affects 1 in about 3,600 live births. It is a rare genetic chromosome abnormality caused by an error in cell division, resulting in an extra eighteenth chromosome. There is no cure or treatment, and statistically, only 5 to 10% of infants born with Edwards syndrome will live past their first birthday, but with severe intellectual disability. For patients with Edwards syndrome and other related rare diseases, new development in cell and gene therapy products show to potentially modify or even cure these severe chronic conditions.

As patients and parent caregiver advocates, there is an inherent sense of urgency to not only find cures or treatment solutions but to also identify measures that might create better health outcomes and establish a better quality of life for individuals living with rare conditions. I believe clinical outcomes are often dismantled by patient communities because patients were not included in the study design. I believe unmeasurable expectations from patient communities stem from patients not knowing or understanding the achievable clinical outcomes or endpoints.

Patient participation in research can help answer health questions that matter most to the patients and their doctors. Having the patient voice not just at the center but at the beginning of clinical study development can yield greater results to all stakeholders, because the clinical outcome goals are consistent and aligned among researchers, investigators, and patient communities. As a patient advocacy organizational leader and parent advocate to a now 5-year-old kindergartener with full trisomy 18, I believe patients can contribute significantly to clinical trials that

are designed to meet their unmet needs and priorities, if they are involved as partners in the research process at an early stage.

Clinical studies should focus on addressing the priorities, preferences, and needs of the affected patient communities and to those who have compromised quality of life. To do this, at patient advocacy organizations, we support data collection and data sharing, but patients and families must also be given opportunities to share their lived experiences of the daily burden of disease and their perspectives regarding unmet needs, therapeutic burdens, and the types of research questions most important to them. Patients with lived experiences expect to be included in the framework development and the overarching landscape of strategy and implementation. Having patient partners in clinical study design and execution can transform the clinical development process from one directed by sponsors and investigators to one driven by the needs of patients and their caregivers.

Thank you so much to the FDA and OTAT for the opportunity to join today's conversation. Thank you.

MS. ROWZEE: Thank you, Sarita. Our next speaker is Donavon Decker.

MR. DECKER: I have no financial disclosures. I was diagnosed with limb-girdle muscular dystrophy 2D 44 years ago. In 1999, I was the first person in the world to do gene therapy for any form of muscular dystrophy, with Dr. Jerry Mendell. The research was supported by the Muscular Dystrophy Association. My injections were done two weeks before Jesse Gelsinger died. There are eight kids in my family. Five of us have limb-girdle 2D, while I have two nieces that have limb-girdle 2I. My sister June was the first person to ever do vascular delivery gene therapy for muscular dystrophy, again with Dr. Mendell.

Two of my sisters, Monica and Mary, have passed away from respiratory failure, which is the leading cause of death in 2D patients. The pictures show my wife and me, Dr. Mendell and me, and my family over 12 years ago. My sisters who lost their battle, Monica and Mary, are on the front right.

Here are a few things the FDA needs to know about limb-girdle muscular dystrophy 2D. Natural history for 2D is not like SMA type 1 or Duchenne. Diagnosis of 2D can be between the ages of 4 and 20. Some start to use a wheelchair full-time before age 10, while I was 42. Breathing issues started in my family in our early 50s. The FDA needs to be open to nonviral gene therapy, since it appears the delivery method addresses the re-dosing issue — gene size in patients with the natural AAV titer. We all know, as today, re-dosing is not possible using AAV, because we don't know how long the titer will remain in the body. Fourteen years after my injection, I still had a titer. We need quicker approval of gene therapy treatments. We've seen how quick vaccines were approved for COVID. And yes, gene therapy's different, but we need the same urgency using gene therapy, as patients are dying.

I'd request the emphasis be put on improving the diaphragm function. I'm told 200 muscles that are involved in walking — 100 of them critical. In contrast, breathing involves 18 muscles, and the majority of that is the diaphragm. If my diaphragm was stronger, that would change my quality of life. Also, trials should include measure outcomes related to the diaphragm strength. There is technology available today to assess diaphragm strength using ultrasound, as presented in the 2016 article of *Journal of Physiology* by doctors Nicholas Whitehead and Stanley Froehner and others.

In closing, the limb-girdle 2D families have built a foundation for gene therapy in muscular dystrophy. We risk our lives but, right now, can't be re-treated, if there is a cure. One patient treated over 7 years ago is now living a normal life — now has normal strength. We need to keep the momentum of that success going. There haven't been any 2D trials for over 6 years. I feel companies shelve research where there are fewer patients and put other diseases and more patients and more money ahead of the people that build research. I believe the companies doing AAV trials have moral and ethical obligation to help these patients if they need to be re-dosed. We deserve better. Thank you.

MS. ROWZEE: Thank you, Donavon. Our next speaker is Colin Werth.

MR. COLIN WERTH: Good afternoon. Thank you for allowing me to speak today. My name is Colin Werth, and I'm a lifelong resident of Farmville, Virginia, located just over an hour west of Richmond. In addition to my work in the IT and marketing field, I am an advocate for the rare disease community. I was diagnosed with Duchenne muscular dystrophy at age 3 in 1998.

Duchenne is the most common form of muscular dystrophy. And as some of the other panelists have mentioned, limb-girdle muscular dystrophy — that's another type. Duchenne is a disease caused by mutations in the dystrophin gene, which is the largest gene in the human body. It is a vital protein for anchoring muscle cells and providing them with needed stability so they don't break down easily. Without this, my muscles get damaged over time and lose strength. Duchenne is a progressive disease which gets worse over time and is in the end fatal. About 1 out of every 5,000 boys has Duchenne, and about 20,000 worldwide are born with it each year. Duchenne mostly affects males and reaches across all races and cultures.

It is estimated that there are about 15,000 boys and men, as well as a few women, living with Duchenne today in the United States. With regards to trial design, it is important to make sure to include the entire patient population living with a certain rare disease. Often, clinical trials for diseases like Duchenne only include younger patients who are still ambulatory. This is because many popular tests to show drug efficacy are related to ambulation, such as climbing stairs, running 10 meters, and walking for 6 minutes. However, this leaves out the patients like me, who are further along in disease progression and are unable to walk anymore. It's important

to make sure we are not forgotten. As patients living with progressive diseases, we are willing to take any treatment we can get to help us. Not being able to walk is one thing, but when you lose your arm function, practically all your independence is taken away. So just make sure, when you're planning trials, to ensure that no one is left out. There's lots of natural history data on Duchenne that could be augmented as a separate trial arm to avoid the need to use placebo-controlled data.

Delaying of patient access to gene therapy, especially in the Duchenne population, is of concern, since once muscle function is lost, it cannot be regained. In addition, it is important we include patients in the clinical trial process more. Including those living with a disease such as Duchenne in the decision-making process is vital to success. People living with rare diseases are the best resource out there, since they understand what it's like to live with a condition firsthand. Patients deserve a say in how these treatments should be studied in order to have the best possible trial outcomes and get novel drugs out there faster.

It's important that the FDA and pharmaceutical companies realize that traveling for medical care and to participate in trials is especially difficult for someone with complex needs and requires use of a wheelchair, like me. Anyone traveling knows how complicated travel logistics can be. And on top of that a complex medical condition, and travel planning becomes much more daunting. If you can, eliminate as much travel as possible, and consider multiple locations around the country, or have labs drawn locally for patients and do follow-up visits virtually. If that is not feasible, make sure to have robust travel assistant programs available to patients. Also consider extended stays in apartments near trial locations so patients don't have to travel back and forth to their home locations.

In closing, not only is gene therapy going to help Duchenne patients, but it can benefit patients living with many other rare diseases, such as those discussed on this panel. Gene therapy can also benefit larger populations as well, such as those affected by diseases including Alzheimer's, Parkinson's, and even cancer. Gene therapy is definitely a technology that will become more and more popular in the coming years. Thank you for your time and for allowing me to speak today.

MS. ROWZEE: Thank you, Colin. Our next speakers are Randy and Maureen Juip.

MS. MAUREEN JUIP: Good afternoon, everyone. My name is Maureen Juip. This is my husband, Randy. We have no financial disclosures. We live in Michigan with our five beautiful children. And when our oldest son, Jake, who's right there in the middle, was in fourth grade, we noticed that he had started to trip a lot, and he was getting really extra clumsy, and he was ultimately diagnosed with a disease called Friedreich's ataxia.

Friedreich's ataxia is a rare disease. It's a prime candidate for gene therapies, because it is a GAA repeat on a single gene. And sadly, it's neurodegenerative. Jake went from being that fourth grader who was really active and playing on his

school's soccer and basketball and lacrosse teams to now being a high school junior who is fully wheelchair-dependent, and he can't even stand without support.

Fortunately, Jake's inner spirit, though, has stayed intact, and he is vice president of his class. He's spearheading an effort to start a recycling program at his school. And so he has so much potential and so much to offer, but FA makes it so much harder for him.

And to add insult to injury, not only has he already lost his balance and his coordination, but the disease is starting to impact his hearing and his vision, and he has hypertrophic cardiomyopathy. And so early access to really innovative treatments is really essential, not only for Jake but for everyone who's living worldwide with Friedreich's ataxia, including our 15-year-old sophomore in high school, Claire, who has also been diagnosed with the disease.

We wanted to start by thanking the FDA for their recent draft guidance that came out in September of 2022, acknowledging the role of children in clinical investigations. Diseases like FA are pediatric diseases that impact a pediatric population, and so it's really important that kids participate in the research around the therapies and, in particular, in the gene therapy trials that are coming on board. And I will let my husband address the rest.

MR. RANDY JUIP: Because of this relentless progression and the awfulness of this disease, and because of the high unmet need, there's no therapy and there's no cure yet. Our patient community and our family have great interest in participating in clinical trials, as you can see from Jake and Claire, including gene therapy trials to come in the future. Our involvement in the design and the execution of these trials is going to be focused on education and a careful evaluation and weighing of the risks and the benefits of each and every proposed trial.

We'd like to comment — on three specific potential concerns with clinical study design and execution: unilateral delivery recommendations, sham surgery as a placebo mechanism, and then the 5-year follow-up requirements in gene therapy trials.

Just addressing briefly the current FDA guidance for industry in gene therapy trials for neurodegenerative diseases, specifically the nonbinding recommendation for unilateral intraparenchymal administration, we would echo the comments we heard from Shandra Trantham earlier in this meeting: Given the unique cerebellar nature of Friedreich ataxia, guidelines requiring or even recommending unilateral delivery wouldn't just fail to de-risk the study, but they wouldn't provide any demonstrable benefit or outcome benefit, even, to the study participants. Accordingly, we, on behalf of our children, would be unwilling to participate in any trial that was designed or required to be designed with a unilateral administration. There's no benefit; there's high risk, including the risk — and we'll talk about this in just a second — that we might be precluded from participating in subsequent trials.

Regarding sham surgery, while we appreciate the historical tradition of placebo control groups, we recognize the willingness of participants in clinical trials to be randomized to different control arms, sham surgery just isn't a reasonable method of achieving control or placebo. First, sham surgery is likely to be ineffective; superficial incision is not going to fool you into thinking you have not had a hole drilled in your skull. It's not an effective method. Secondly, it's essentially all risk to the participant, and it's no benefit, especially when you take into consideration the high risk of general anesthesia that's associated with FA. And then third, we have amazing natural history data, especially in Friedreich ataxia but in other rare diseases, and that's very powerful stuff. So we'd urge the FDA to consider guidance that weighs the power of natural history studies over sham surgery as a control method.

Last, probably the most salient point from our perspective, as parents of two kids with FA, is the design of clinical trials with a very long 5-year follow-up period.

The progression of this disease is breathtaking. Jake and Claire are shown in this slide. Five years ago, Jake's now fully dependent on a wheelchair. Having a child precluded from participating in other clinical trials because of a 5-year waiting period, even if those trials are indicated because of the disease progression in other systems, it's just untenable, and it's arguably unethical. As a rare disease population, we have a limited patient population. We'd urge the FDA to work with FARA, our advocacy group, and industry partners to develop guidance that allows or even encourages flexibility in approach to follow-up. Thank you for this opportunity. We're very motivated by hope and the potential for forward progress and exchanges, and exchanges like this really bolster that hope. I think by working together with FDA and industry and other advocacy groups, along with the families and the patients, we can really move forward together to our mutual benefit and mutual success. Thank you for this opportunity.

MS. JUIP: Thank you.

MS. ROWZEE: Thank you, Randy and Maureen. Our final speaker for Session 2 is Barb Ballard.

MS. BALLARD: I'd like to thank the agency for this opportunity to speak today. My name is Barb Ballard. I am currently the director for SCID, Angels for Life Foundation, where I advocate for patients with severe combined immune deficiency, usually referred to as SCID. My disclosure is that SCID Angels is a paid consultant to MustangBio. At one time, I was a consultant to the cellular tissue and gene therapies advisories committees also. I am the mother of a patient with X-linked SCID.

My son passed away in 2019 at the age of 25. Prior to that time, he had received three bone marrow transplants. At the time of his passing, we had already collected stem cells from him to use for gene therapy. In his case, this was his only remaining option, and we knew this would be a rescue attempt. He passed away before we

could begin the process necessary to receive his corrected cells. SCID is one of those rare diseases that is often first to be studied in clinical trials. Untreated, it is fatal by the time the patient is 2 years old. But to date, treatment is not a cure.

Many SCID patients treated right after birth still lead medically complicated lives. We know that better treatments are needed, and as parents, we are willing to educate ourselves to learn about these complicated medical procedures, which could lead to a higher quality of life for our children. We approach gene therapy knowing it is not a magic wand which will take away all risk of complications, but we have seen that it can lead to healthier and longer lives for them.

Of great concern to us is the fact that as these new cellular therapies try to follow the historic path previously forged by new and innovative treatments progressing to the marketplace to become standards of care, the costs associated with these cellular therapies are rising astronomically.

SCID gene therapy clinical trials at the research level are showing that such therapies provide better outcomes than approved treatment options. Ironically, companies are unable to bring the products to the market due to the high costs associated with meeting newer and more quantitative evidential requirements for gaining approval. The result has been that some companies have walked away, abandoning patients who are waiting for treatment. The children shown on my slide are a handful of those waiting on the reopening of ADA-SCID gene therapy after just such an occurrence. Some of these children have now been waiting 5 years. A few have not survived the wait.

Some will argue that these children are in a position to continue to wait, because they can be maintained using an enzyme replacement therapy, which is itself an orphan drug. The use of this drug does not come without its own complications and risks. Yet because it's an orphan drug and not a cellular therapy, it is available. Why is it that there is not more financial incentive to orphan drug status when new cellular therapies which could save the lives of those with a rare disease are possible, but the cost to produce the therapy becomes unsustainable?

Could those therapies for which assay tests are not practical be encouraged to utilize a different method to evidence successful treatment? Can we find a way to fast-track these clinically successful therapies? Are we going to allow the pharmaceutical industries to walk away from these patients because the therapy is not economically viable? What about the viability of the life of a child? We all know that pharmaceutical companies are willing to invest in rare disease treatments that they feel they can expand into other, more lucrative areas. How do we make sure that those patients who require a viable treatment which cannot be expanded to other large disease groups such as cancer are not left out? Thank you for your time.

MS. ROWZEE: Thank you, Barb. And again, thank you to all of our Session 2 speakers for sharing your perspectives on clinical study design and execution. I believe we do have a question from the FDA panel.

DR. YUXIA JIA: Hi, this is Yuxia Jia. I'm one of the medical officers and medical oncologists here. Our panelists today here from the FDA are all physicians, and we do reviews and try to help with the development. In the meantime, many of us still continue medical practice and caring for patients. So this session is very helpful in hearing your voices and your perspectives in terms of clinical and patient experience and barriers to participating in clinical trials. Some of the speakers today already mentioned barriers to participating in trials. This is critical in terms of expediting drug development, especially in rare diseases, like many cases we've heard about today. So if I may ask for your suggestion, maybe in just the one key barrier to participating in gene therapy trials, and from your perspective, each speakers, if you could share — some even mentioned, but it's nice to hear them again. Thank you.

MS. ROWZEE: I think Yuxia is asking that — if folks could speak to one key barrier in participating in a gene therapy study or clinical trial.

MS. BRYANT KNUDSON: Thank you so much. The placebo-controlled trial designed for ultra-rare diseases is a huge impediment for, I think, any rare disease, especially with the limb-girdle muscular dystrophies with some of our subtypes being so ultra-rare. It really discourages any other drug developers into our space when they see how ultra-rare it is. And then when the traditional placebo control design is the requirement, it really is just going to delay for us. So using other innovative methods — and especially since we have so many natural history studies spanning 15 years for some of our forms, I'll just end with this: We encourage patients all the time to do natural history studies; we're always encouraging that, but what good are they if we can't use them in these innovative ways?

MS. ROWZEE: Thanks, Kathryn.

MS. BALLARD: Yes. Kind of repeating what I said before when it comes down to the cost viability of a study. We're losing the pharmaceutical industries because of the costs of getting things through FDA and getting them approved. It's great to be able to have a clinical trial. We have a clinical trial with 50 children successfully treated that was dropped by the pharmaceutical company. These are areas where we really need to rethink the process of how we bring things to market, how they get approved and onto the market, because the traditional method is not working for gene therapy and cellular therapies. That's all.

MS. ROWZEE: Thanks, Barb.

MS. DECONTI: Thank you for the question. I think from my perspective, it's definitely the lack right now of gene therapy trials for my son to participate in. He has LGMD2D,

and there's nothing available. But similar to what Kathryn mentioned and others, just more innovative ways aside from placebo or high dose/low dose being available. When a treatment is ready for my son, I think it's something critical. We are in a place right now where there's so much new and innovative medicine coming out every single day. I think gene therapy is certainly there, but we just need to think of different ways to bring success on patients.

MS. ROWZEE: Thank you, Rachel. I think I'll call on Donavon and the Juips, and then Corrin.

MR. DECKER: I guess the thing I'd like to add is, the SMA trial was approved with not that many patients. And yes, they could see really quick improvement. But I think in these ultra-rare diseases, you're not going to be able to see — it's not going to be feasible to have 50 patients or even 30 patients for a 2D trial, so I think the FDA needs to be aware of that and open to smaller trials that can lead to approval. Thank you.

MS. ROWZEE: Thank you. And then the Juips.

MR. JUIP: Yeah, thanks for the question. I think — we chatted, and for us, it would be the weighing of benefit to a single system. I think, as was mentioned by one of the panelists before, having a single gene therapy that takes care of the entire disease is probably too big of an ask right now. Most gene therapies in the early phase are going to focus on one system or one set of symptoms, and everyone individually is going to have to weigh what symptom or what system bothers them or concerns them the most. I think the barrier for entry to us is not knowing the exact progression of this disease, and because of the design of a trial that would require a long waiting period — 5 years perhaps — that might preclude you from participating in other clinical trials, both gene therapy and otherwise. I think that's really the biggest barrier to us, especially in a progressive disease, where the symptoms will continue to progress, and 1, 2, 3, 5 years down the road, another system might merit participation in a different clinical trial. That piece of the study design, the follow-up period, is the biggest barrier to entry for us, I think.

MS. ROWZEE: All right. Thank you for your comments. Unfortunately, we're going to have to move into our next session.

We have two remaining sessions. We're now moving into the third session, on current tools or methods to capture patient experience data and any existing challenges or gaps to capturing patient experience data. I believe we have five speakers now in this session. Each speaker will have 4 minutes.

Our first speaker is Claudia Fennell.

MS. FENNELL: Good afternoon. Thank you so much for hearing patient, family perspectives on this issue today. My name is Claudia Fennell, and I have no financial disclosures. My youngest daughter that you see here, Penelope, was

diagnosed with CLN2 Batten disease in October of 2017, when she was 3. Earlier today, you heard from other members of my CLN2 community. As was highlighted, this is a fatal neurodegenerative disorder that begins in toddlerhood, and within a few months to years results in a need for complex medical care and total dependence on caregivers for all aspects of living.

I would like to paint a picture of what capturing patient experience data means in a population like ours. It's small, resource-limited, and in which families are often caring for other young siblings, due to the age of onset, and even multiple affected children. Since the approval of an enzyme replacement therapy in 2017, our kids are aging into increased contact with care teams and longer-term health management. Our touchpoints to capture and share data break down into three primary areas: our doctors, other CLN2 parents, and occasionally biotech company surveys.

However, information is usually privileged or stays with families and only rarely feeds into the drug development process in a transparent way. Our community is eager to share data in any way that would accelerate clinical trial approval.

Our toolkit and resources are limited. If a child is well enough to travel, some families share data through an ongoing drug sponsor study following patients receiving ERT. This takes the form of behavior, quality-of-life, and sleep surveys and basic functional and cognitive testing.

Some families complete questionnaires and have their child participate in one major natural history study, although participation is very limited, especially since COVID. Other quantitative tests tracking seizure activity and vision loss are voluntary, they're non-standardized and performed either in response to an immediate health issue or if the family is simply curious. Families with children that are more progressed in disease stop participating and testing as the progression towards the end of life becomes clear and therapeutic and medical interventions become ineffective.

None of this data truly captures some aspects of the patient experience, however — things that define the feel of living with CLN2, if you will. So I'll jump over to the right to examples of gaps in data that are meaningful when thinking about gene therapy trials, and I'm sure that these things apply to other diseases, things like musculoskeletal issues, progressive dystonia, and ataxia and its impact on quality of life, and understanding of the multiple phenotypes within CLN2 Batten — verbal and nonverbal communication challenges, progressive dementia and how that affects the family, the financial burden of caring for a Batten child, and finally the burden of biweekly enzyme replacement therapy, which is our only treatment option.

The challenges to filling some of these gaps are multifaceted. The financial burden in our community lies primarily with our families or patient advocacy group to capture data. Clinicians often do not see the point, which highlights a disconnect between frontline care and drug development. Our communities' experience

highlight inequity in resources and the multifaceted and sort of intangible destruction of a fatal disorder. Our hope is that families can partner with researchers, industry, and the FDA to address these factors and funnel patient experience data into the evaluation of gene therapy products and the design of clinical trials. Thank you for your time today.

MS. ROWZEE: Thank you so much, Claudia. Our next speaker is Ying Huang.

DR. YING HUANG: Hello, everyone. I'm Ying Huang. I am a GYN/oncologist. I'm also a patient and a patient relative. My mom has cancer and has been through the treatment, and that's why I am very interested in gene therapy and the future of gene therapy. As a researcher, I realize that gene therapy, mostly the recruiting process, is very challenging due to the nature of the studies that most likely are focused on the devastating disease or the disease in the devastating stages around the screening, recruiting, to consenting, to receiving the intervention.

The study team and the participants like us have been putting in a lot of time and effort. However, through our journey, we also learned that there are some participants coming together with the common goal to challenge the science and trying to contribute. They sometimes expire prior to the treatment that could be deployed on them. We are wondering if the data collected from the participants — even they failed to receive the intervention — have been systematically evaluated during the regulatory decision-making process by FDA and the study teams.

Also, what we would like to know a lot more is — receive guidance from the FDA as a patient and also as a researcher. What are the FDA's thoughts and guidance on how to use the data collected from the patients even if they are not able to receive the gene therapy? They may have some features or some important information that could be utilized to impact future study design and strategies for the inclusion and exclusion criteria.

My second part of comments is that gene therapy is relatively new. And I know of many experts, especially regarding the long-term adverse events. The mandate of long-term follow-up is very important, and we appreciate that. We are looking for the PRO tools designed specifically for gene therapy recipients to capture potential long-term adverse events as well as some outcome information. Again, as a patient and the researcher, we would like to know a little bit more about FDA's vision of the patient-reported outcome tools operated was the post-marketing surveillance tool, as well as research capturing system. What are the best practice strategies and the future visions from FDA? Thank you.

MS. ROWZEE: Thank you, Ying. Our next speaker is Monica Dudley-Weldon.

MS. MONICA DUDLEY-WELDON: I'm Monica Dudley-Weldon, and I am first the mother of a child with SYNGAP1, and I also serve as the president/CEO of the SYNGAP1 Foundation, and I have no financial disclosures. And just to kind of echo everyone

and the topics, I have a little bit of mix. It's all intertwined. I'll go ahead and read my comment, and hopefully, I can add a few new little twists and ideas about engagement and thinking about moving forward with data.

I agree with the fact that our patients need more education, especially around risks and benefits. Every family has a different view of what value is. Families make observations based on their quality of life. Many times, they consider the most minimal potential benefit significant and believe decisions between risk and benefit are equally important. If the benefit shows progress is slow but visible, and there is no regression, most families will outweigh the risk and moving forward with the gene therapy. Patient populations understand the thought processes around decision making and traditional therapies and treatments.

Due to the high-paced evolution of and innovation of gene therapies, patients and families do not often understand enough about the process of gene therapy to make informed decisions. The situation is a complex one, since there is the problem of long-term side effects that are unknown and echo what the doctor just said. There are common misconceptions about the genome and the need to be accessible to more information and education to patients and caregivers, patients understanding the basic needs of what genetics are and fixing the problem and I say quote-unquote as I revert back to the word 'cure.'

Many, of course, don't understand the one-and-done. Unknowing, they participate in, for example, *N-of-1* trials, and it can disqualify them from future trials. Navigating from this situation is already a difficult one in rare disease due to the lack of numbers and qualifying patients that meet the inclusion criteria for future clinical trials — and engaging those patients to be able to have a better thought process and including them forward and to larger genetic therapy trials.

Neurological disorders. Crossing the blood-brain barrier, due to the nature of gene therapy products and cell-mediated therapies, many concerns of caregivers and patients alike are aware of the high probability of a gene therapy working and genetically linked neurological disorders — reverting to the point made back in regard to patient education, many typically don't understand the three aspects of risk assessment and the data that goes into creating a dose design and the delivery, determining whether or not a patient will participate, and you can engage them better in learning more about a gene therapy and providing data for these natural history studies.

Administering gene therapy for neurological disorders is extremely difficult. New techniques developed, such as iPSC stem cell lines from patients with genetic disorders, are a valuable step forward in creating disease models for drug testing and validation of gene therapies. One of the drawbacks, however, is calculating the dose and determining specific areas of the brain to attempt treating the whole brain. How do we determine the process, is by de-risking.

Some of the things that our patients brought up are the core ingredient is the design. Many of our patients are wondering how do we participate and capture the data of families involved, and they are unable to finish some of the needed measured steps because of sensory issues with these kids that have autism behavior issues — and just considering how will we get these children to do some of the things even if we can get them into the procedure.

MS. ROWZEE: Wonderful. Thank you, Monica.

Our first three speakers, Claudia, Ying, and Monica — if you're available, we do have a question or two from our FDA panelists and I'll invite them to join as well. Dr. Gatti, do you have a question for our speakers?

DR. JASMINE GATTI: Yes, hello. Thank you so much for your advocacy work and sharing all your personal stories, as well as the very, very excellent slides that you have. I know that education was mentioned in not only this session but in earlier sessions by a few of the presenters, and an earlier presenter had mentioned that in his search for information about whether or not to go forward with gene therapy, he suggested that FDA create some reading materials. And so, I noted the recent presenter mentioned some educational things as well.

So, my question is twofold. One is, in your search for information, if FDA could do something like that, what were some of the challenges you had in finding that information? And secondly, what was difficult to understand? Thank you.

MS. DUDLEY-WELDON: I'll take a shot at your question. I'm a teacher by trade, and I also have a science background. I would have to say that a lot of our families — I mean, there's an equity problem. I mean, you have people that have different levels of education. Of course, interest; you've also got the emotional component. I would have to say a lot of the science, the basic genetics, understanding — it all starts with the basics, I believe. And I think a lot of the families are missing the basics of how this works.

As a mom, you want that treatment, and I believe desperation and then also just the fear — I think the fear of the unknown of side effects, because how do we measure side effects of a one-and-done study? And you know that when you are giving a dose, that's it. It either works or it doesn't. And so, I think there are a lot of unknowns, that causes fear — the lack of education, because gene therapy is in its infancy, and there is such a rush. And I'll probably get in trouble for saying this, but sometimes you want science to be slow, but you don't want it to be slow. And gene therapy, I think, is one of those that — we are messing with DNA; we are messing with RNA, and we really have to think. And natural history studies — I'm going to echo everybody who said natural history studies are very important. Epidemiology is very important. But getting that message across to the general population is incredibly difficult. And I'm trying to figure out how to get it across.

MS. FENNELL: I'll take a quick stab at this as well. I want to echo the point about equity. I think there's sometimes language barriers. There are patients that are scattered all over the place and don't necessarily come into contact with people that have really introductory information about gene therapy, so trying to reach that population. For our CLN2 patients, a lot of them, their care is based in a hospital setting. And it's quite often one after another sort of urgent medical situation.

And what we find — my personal experience, especially over the last 5 years with my daughter's diagnosis, was that clinicians themselves don't really know much, and so I think there's a gap between what the FDA wants the medical professionals to know and what sort of, as I mentioned before, frontline-type care workers that are dealing with medically complex children can communicate to their patients. I also second the point that advocacy groups play a big role in providing information as a neutral party and, like ours, one whose resources are extremely small, very little funding. That information is not coming from a national organization, for sure. That's my two cents.

DR. HUANG: This is Ying. I would echo one of the speakers' comments that, as someone whose first language is not English, navigating through the FDA's website and finding out the specific information regarding some therapy is a little bit challenging. Also, I find out the, like, conference videos, workshop videos, and educational series that FDA posted on YouTube are very helpful and easy to understand and follow. You can go back to watch and learn again. If it's possible for FDA to develop some of educational material, I think that this kind of video will be very interesting and very useful. Thank you.

MS. ROWZEE: Thank you. I believe that might be our only question from the FDA panel. Again, I just wanted to thank our speakers for sharing their perspectives and also for responding to our questions.

Our fourth and final session of the day is on approaches to leveraging existing tools or opportunities for unique tools to capture patient experience data in gene therapy studies. We have five speakers scheduled for this session. Again, each speaker will have 4 minutes.

Our first speaker is Ryan Fischer.

MR. FISCHER: Thank you for the invitation to speak today and for convening this important forum. My name is Ryan Fischer, and I serve as chief advocacy officer for Parent Project Muscular Dystrophy, or PPMD. I want to thank Colin, Jen, and Tushar for providing such powerful testimony on behalf of our community earlier today.

My comments will address unique tools and approaches related to how sponsors and FDA can apply patient experience data in gene therapy studies. I want to first highlight our community-led therapy development guidance.

In 2014 — and you can go to the next slide — in 2014, we led the creation of the first-ever patient group-initiated draft guidance on Duchenne. Our goal was to provide a roadmap for companies developing therapies for our community. And the completed guidance was submitted to FDA and posted to the docket, and FDA later released their own guidance, which was finalized in 2018. Since that time, much progress has been made in Duchenne, including five FDA approvals and a growing therapeutic pipeline, including several gene therapies, prompting our community to reconvene and update the guidance document with new knowledge. The guidance includes two new sections, one on cardiac and one on gene therapy. We formally submitted the update in September and are hopeful that CBER and CDER will utilize and disseminate the community-led document internally.

An example of patient experience data I'd like to discuss is patient preference information.

We've been conducting preference studies since 2014. Our work is aimed at quantifying how patients and caregivers think and feel about emerging therapies and their priorities for new treatment targets. With such published data in hand, we can better advocate on behalf of our community. Through testing various methodologies, we have demonstrated that preference research can be rigorously performed in our population and may be adapted for other rare diseases. This is all about advancing the science of patient input. In terms of learnings from these studies, results have consistently shown that Duchenne patients and caregivers have demonstrated a tolerance for even serious risks and uncertainty in exchange for a therapy that could slow disease progression. This is a message you've heard consistently through patient testimony today.

On the right, you can see two examples using different methods from our studies. In both, participants chose tradeoffs based on treatment attributes included in the surveys, which provide quantifiable preference data on how patients and caregivers weigh the value of the therapy and its options. Which attributes of emerging therapy profiles are most meaningful and important for those making treatment decisions? Such depictions should be informative for regulatory considerations, for it is they who live with the decision making and they who live with the benefits and risks.

We've continued to adapt and advance the use of different preference methods over time as PFDD guidances emerge. Given today's topic, I would like to highlight our work in gene therapy, looking at maximum acceptable risk that is tolerable to adults with Duchenne and caregivers for non-curative, time-limited gene therapy.

On the left side, you see the setup for the experiment. In the survey, we proposed a hypothetical gene therapy treatment benefit of up to 10 years of slowing disease progression. We then asked participants to imagine their doctor proposes gene therapy as a treatment option, but there's a risk of death following therapy administration. They're then presented with a series of risks, starting with the

lowest risk, presented as 1 in 2,000, and increasing up to 200 out of 2,000 risk. They're asked to choose if they would take gene therapy across different stages of disease, which also consider linkage to time points in disease progression. The risk levels increase if they indicate they'd be willing to accept the risk presented.

On the right, you see the results. The darker the blue, the higher the tolerance for risk chosen. The results clearly show and highlight that risk tolerance increases with disease progression, the highest tolerance in the last year of people being able to feed themselves, something Colin pointed out in his testimony. Though some heterogeneity is seen, the overall results demonstrate a clear willingness by most participants to accept some level of risk — even a serious risk, like the risk of death — in exchange for a potential benefit of even slowing disease progression.

It's our hope that regulators will incorporate such patient experience data into decision making, including labeling of future gene therapy products, so that practitioners can consider individual and aggregate preference data in their care decisions.

We're currently working on a second study. The science has evolved, and preferences change over time. These methods should be used over time. We think they're a really helpful tool. We urge FDA to incorporate robust patient experience data, such as the two examples presented, into gene therapy study designs and regulatory decision making within PFDD and its contract, which is stimulating the pipeline across so many conditions. I thank you for the time.

MS. ROWZEE: Thanks, Ryan. Our next speaker is Jennifer Farmer.

MS. JENNIFER FARMER: Thank you for the opportunity to speak today. I'm Jennifer Farmer, chief executive officer of the Friedreich's Ataxia Research Alliance, or FARA. I have no financial disclosures. FARA's a research advocacy organization. Our mission is to treat and cure Friedreich's ataxia, or FA, by marshaling and focusing global resources and relationships. FA is a rare, inherited, multisystem condition that affects about 4,000 individuals in the U.S. In all cases, FA is a degenerative, progressive, debilitating disease, and currently there are no approved treatments.

You have heard from several members of our community today — Shandra, Randy, and Maureen — providing comments and feedback on considerations for gene therapy clinical trials. I'm here today to ask that we identify mechanisms for reducing to practice the use of natural history and non-interventional data, as suggested in various FDA guidance documents, in the development of innovative and adaptive trial designs, including those where such data can supplement control or comparator arms. FARA has worked with the clinical research community to carefully study and understand the natural history of FA.

There's an ongoing prospective, longitudinal, non-interventional, observational trial that's entering its 20th year with nearly 1,500 individuals enrolled. The participants in the trial represent the overall FA population. And given the size and duration of the trial, there's the ability to also evaluate subgroups. All the endpoints are prespecified with standardized collection procedures. All the data has been collected and curated in a 21 CFR Part 11-compliant electronic data capture system. The investigators and sites involved in the study are also experienced in interventional trials in FA, using many of the same assessments.

This non-interventional study has contributed to the understanding of natural history of disease, development of clinical outcome assessments, patient-reported outcome measures, and informed clinical trial designs published in more than 25 peer-reviewed manuscripts. In addition, the data from this study and other clinical trials are available in the Rare Disease Cures Accelerator-Data and Analytics Platform, an FDA-supported initiative that provides a centralized and standardized infrastructure for sharing and analysis of such datasets.

Many more details can be provided about this trial and the practices and procedures employed to ensure data integrity and interpretability. FDA guidance documents, including rare diseases, natural history studies for drug development and human gene therapy for neurodegenerative diseases, and many others, acknowledged the opportunities for using such natural history data in clinical development. However, there seems to be a gap in reducing this to practice, especially when considering leveraging such datasets in control or comparator arms for trials.

We're in agreement with FDA guidance and recommendations that optimal study design is randomized and controlled so that results can be quickly and accurately interpreted and that innovative and adaptive designs may also be employed to facilitate product development. We would like to work with FDA to identify mechanisms, where such trials and datasets can be used to inform and supplement adaptive design approaches such as Bayesian methods of borrowing historical data. These novel methods of borrowing data to supplement control or comparator arms can address some of the challenges in conducting trials in rare diseases — specifically, reducing the size of placebo arms and overall number of participants, time, and resources to conduct the trials.

We're encouraged by the recent announcement that's elevated and increased resources for OTAT. It's critical that you have the human and technology resources needed to meet the growing demands of translating, evaluating, and approving these novel therapies. I would like to thank all the participants today who've shared their experiences and are continuing to participate in the development of gene therapies for all of these diseases and many others. Thank you.

MS. ROWZEE: Thank you, Jennifer. Our next speaker is Annie Kennedy.

MS. ANNIE KENNEDY: Great. Thank you so much to FDA for convening this incredibly powerful forum today. My name is Annie Kennedy, and I'm really proud to be here on behalf of the broad rare disease community and the EveryLife Foundation. EveryLife is a rare disease policy organization that understands that no disease is too rare to deserve treatment and that rare disease therapy should be safe, effective, and granted expedited development.

On the day that the 21st Century Cures Act was signed into law, Dr. Janet Woodcock observed that the bill would codify additional core patient engagement provisions and further enshrine PFDD as a part of the FDA's core mission. Since that time, many more significant milestones have been achieved as the science of PFDD continues to evolve and transform the way stakeholders engage around therapy development. Notably, of the more than 70 PFDD meetings convened to date, at least half have focused on rare diseases. We've benefited from the implementation of the patient experience data table as a part of drug approval packages, providing a new level of transparency and engagement between the review division and relevant stakeholders around the integration of patient experience data within regulatory review.

And the issuance of numerous guidances that are informing patient engagement and patient-focused drug development activities for drugs, cell- and gene-based therapies, diagnostics, and medical devices have been critical to expanding our rare disease development pipelines and refining review perspective. Earlier this year, EveryLife partnered with the National Health Council, pharma, bio, and many of our partners in the rare disease space to publish the guide to patient involvement in rare disease therapy development, a community-led assessment of the guidances informing the inclusion of patient experience data within rare disease therapy development.

By instituting a structured approach to listen to the voice, experiences, and perspective of the patient in a meaningful way, the FDA has demonstrated its commitment to patient-oriented translational science and to ensuring appropriate processes are in place to quantify the perspective of the patient and caregiver. As we look to the future of rare disease therapy development, especially as it pertains to cell and gene therapies, as a coalition we offer the following two categorical insights.

First, a June 2021 independent report required by Congress and commissioned by the FDA recognized FDA's commitment to advancing PFDD but also specifically analyzed whether and how FDA uses patient experience data and applications. This report recommended that FDA provide more information to stakeholders about how the agency uses this important data to inform regulatory decision making. Additionally, the PDUFA VII agreement was an incredible reflection of FDA's commitment to enhancing the rare disease regulatory efforts and a signaling of the advancement of PFDD within CBER. However, it did not explicitly mention specific

ongoing commitments to evolving the inclusion of patient experience data within decision making.

To address these remaining gaps, we encourage CBER to provide additional insights as to what additional enhancements are being planned internally to ensure that patient experience data and the patient voice continue to have a growing impact on the development and review of new cell and gene therapies. As an example, as we consider the evolution of the application of patient experience data, we would urge CBER to consider developing processes which will incorporate PFDD-related findings from review activities into product labeling.

The second insight: While the numerous guidances that are informing patient engagement and patient-focused drug development activities have been quite positive, the rare disease community has experienced very little concordance between how CDER and CBER approach therapeutic development within our respective disease spaces. Some rare diseases, for example, may have a gene therapy and a small drug in development at the same time, meaning different divisions within the FDA are involved in parallel engagements with disease community experts.

Navigating these complex issues requires its own set of expertise in rare disease product development and review, expertise and experience that is inconsistently distributed within currently existing organizational structures, in which a Rare Disease Center of Excellence could serve to help bridge health and expand. We recommend that FDA lay out clear actions that it will take in the near term to help reconcile different approaches between these two centers and to help standardize the agency's rare disease guidance, PFDD meetings, and review activities more broadly.

Our rare disease community recognizes the many challenges and complexities of rare disease therapy development. We urge CBER to continue to embrace the regulatory flexibilities and many tools FDA has at hand to overcome these challenges in order to bring these promising therapies to patients as soon as possible. Novel trial designs, including alternatives to placebos, the use of surrogate biomarkers, the expansion of the complex innate design program, and platform approaches — if we do not embrace these regulatory tools, these therapies may never be developed, and millions of rare disease patients will be left without treatment options.

At least we've heard throughout the day, significant data collection efforts have been undertaken by stakeholders to quantify patient and caregiver tolerance for risk and uncertainty as related to specific diseases, cell populations, and experimental therapies. We must ensure that this patient preference data is considered carefully as a part of the regulatory review and the benefit/risk framework.

Thank you for your tireless work on behalf of our rare disease community and for your commitment to ensuring that the promise of today's cell and gene therapy

pipelines will change health outcomes for this current generation of rare disease patients. Thank you.

MS. ROWZEE: Thank you, Annie. Our next speaker is Andrew Wayne.

MR. WAYNE: Hello, guys. Thank you so much for allowing me to speak today. Mine is going to look a little bit different than everybody else. I was lucky enough, actually 4 years ago to the day, to receive Roctavian, a gene therapy drug to treat my severe hemophilia A. And it's my hope that by participating today that we look at the whole patient when considering the benefits of gene therapies, maybe even looking beyond things that we don't think to measure. My life and my gene therapy story is a lot more than kind of these numbers and statistics that get reported.

There's kind of a story, really, but I spent much of my youth and teenage years wanting to feel normal. Hemophilia was not something I wanted to talk about. And I was not interested in missing a pickup basketball game or a backyard football game, even if that meant extra infusions, bleeds, or playing through pain. But I was 26 years old when I was approached by a doctor about gene therapy. By that time, the pickup basketball games were few and far between. My weekly prophylaxis regimen was working extremely well, and I hadn't had a bleed in years. The prospect of not needing to infuse anymore was intriguing, but I honestly questioned how much this new therapy would affect me.

Driving home that day from the doctor, though, I thought about my 10-year-old self giving up baseball, because the kids started to throw a lot harder and my parents were concerned about me taking a pitch to the head. I thought about my 14-year-old self giving up my dream of playing high school basketball, because my joints and factor level couldn't keep up with the 4 days of practice each week, and I thought of my 17-year-old self opting to attend a college closer to home, largely to avoid having to keep all my factoring supplies in a dorm room. I hadn't thought about that kid in years. But at that moment, that was all I could think about.

And it was for that kid that I chose gene therapy, not for the 27-year-old that was about to go on this journey, and to try to make a difference in the lives of others, particularly young people living with hemophilia. My mind was made up, and I anxiously awaited results to see if I was eligible for the therapy. Date was set, and like I said, 4 years ago to the day, I headed to the University of Michigan for my dose of Roctavian.

After I got it done, I was kind of this, "Hurry up and wait! Is it going to work? How well is it going to work?" Five weeks after receiving the treatment, I was shaving, getting ready for a Christmas party — cut myself shaving. Typically, that was going to mean blood — rushed to the refrigerator to grab my medicine, start an IV — and before I could even get it out, I had caught it. Kind of this surreal moment: I smiled and put the medicine back in the fridge. Factor levels continue to climb, and my right elbow, my target joint, stopped aching.

That kid in me that I'd forgotten about years ago said, "It's time to really test this out." Basketball was my first stop, and after many hourlong sessions of games, my knees, ankles, and elbows felt great. I just wanted to keep trying things. I always wanted to run in the Louisville mini-marathon before the Kentucky Derby — goes right through Churchill Downs. I tried to run it several times, years prior to gene therapy, but was derailed with knee and ankle injuries. My morning infusion routine was replaced with time to walk and jog and kind of train.

That kid who had constantly felt left out finally got in the game, and I completed 13.1 miles that spring morning in 2019. Many trips would occur in 2019, as I was taking full advantage of not needing to bring factoring supplies on a plane or my body feeling sore after a long road trip. Eventually, this became my new normal. Doing all the fun stuff was amazing, but there are so many extraordinary moments in the ordinary: playing with my nephew, cooking breakfast for my family in the morning, picking up my daughter and rolling around on the floor with her, all without thinking about infusing, setting out factor, or pain.

I was hoping to experience some convenience from gene therapy and to help some kids with hemophilia. I was not expecting to heal the kid that had to stop doing what he loved years ago. I wasn't expecting to feel as good as I feel, and I certainly wasn't expecting all the little things in my day-to-day life that gene therapy has changed. This session is about opportunities to capture patient experience data in gene therapy trials. There's lots, lots of blood work and trial measures for me that you can look at that show you how well this works. But that won't tell you the whole story; the impact it's had on my life is so far beyond the data. And I hope I conveyed some of that today. Thank you.

MS. ROWZEE: Thank you, Andrew. Our final speaker for Session 4 is Amanda Beedle.

MS. AMANDA BEEDLE: Hello. Thank you, Andrew, prior speaker; such a powerful story you shared. Hello, my name is Amanda Beedle. I am speaking today on behalf of our CLN2 Batten community at large. I have no disclosures, financial or otherwise, to share. Professionally, I happen to have a registered nursing career that spans the course of over a decade. Much of that experience was spent directly supervising the care of our nation's veterans. With my children's own rare diagnosis in December of 2020, I found myself on the other side of the bedside in a way I never before could have imagined or fully understood.

Here are my husband and I, our two beautiful daughters, who both happen to be living with CLN2. As you carefully consider therapies for a multitude of rare and terminal conditions, I want to offer recognition and gratitude toward the detailed review process you are responsible for. As part of our greater CLN2 community, I am here today to share with you some of our perspectives regarding utilizing both existing and potential tools in capturing patient experience data during gene therapy studies. Our community desires to closely partner with researchers and clinicians.

Our community is aware of existing data entry and targeting tools, and be it through artificial intelligence technologies, the future of database entry and collections during gene therapy studies continues to develop.

Speaking specifically to trial design, we as a community recognize introducing placebos and sham cohorts is unethical. It is unethical to withhold a potentially helpful therapeutic in a population with such a devastating decline. How do we as a community pair with multiple approaches? Could biomarkers be part of this answer? If so, how may we accelerate this process as biomarkers are continually being reviewed and considered by scientists? Accelerating this process could include appointing a surrogate biomarker reasonably likely to predict a drug's clinical benefit. We recognize that most gene therapy candidates are currently using the same AAV vector of pre-existing approved treatments; the proof of vector has already been established. How am I using this pre-existing data work to expedite future therapies? We must take into consideration that individual data can be highly variable due to different phenotypes, as well as walking in new natural history in a post-cerliponase alfa world — this is speaking specifically to CLN2.

Data must be obtained in reasonable time frames. Our children do not have years to wait for long-term data collection for possible treatment modalities to advance through the approval process. We recognize it as blindness or blindness, regardless. It is death or death, regardless. As a community, we welcome utilizing a new approach combining both preclinical endpoints and patient experience data. We want to be asked what is clinically meaningful to us in our children. How do we reconcile identifying one narrow talking endpoint with the overall patient-reported outcomes and outcomes that are meaningful to us as patient caregivers?

We ultimately know our children the best and want what makes the strongest impact in their lives. How do we take into consideration that the patient is his or her best control? As our CLN2 community has previously identified during our March presentation, the health, emotional, and financial implications are immense in living life affected by a CLN2 diagnosis. With the hope of clinical trials opening, we gladly assume and accept this additional responsibility of extensive data collection. Ultimately, this is not just data on the page. This is our children's lives.

Time is of the essence. By whichever means data is collected by both patient caregivers and clinicians, the process must be simplified, standardized, and streamlined. Our community never wants to be in a position where years, even decades of data collection are later discarded.

As Suzette James had first shared, our children and families face a brutal and always fatal personal pandemic. Our children need help. Thank you for the opportunity to present and for taking our voices into consideration.

MS. ROWZEE: Thank you, Amanda, and to all of our Session 4 panelists.

DR. HART: Thank you. So once again, thank you all for sharing your perspectives and your stories. And we appreciate the patient experience information that we get, obviously, today from the patient-focused drug development, from the listening sessions, from the outreach that we do in all forms.

There's been a lot of focus on patient experience data as it relates to efficacy. I have a question related to safety, because this is something that everybody needs to consider in the early part, as far as whether you're going to participate in a clinical trial, when you weigh the benefits and risks, and then later on, as we get further in the development as far as approval.

And so, as we discussed tools, what thoughts do you have as far as tools to understand tolerance for risk and the patient perspective and anything that can be quantifiable to provide that patient perspective on acceptable risk, particularly as it relates to different levels of potential benefits from products?

MR. FISCHER: I'm happy to start. This is Ryan Fischer from PPMD. I think some of what I discussed in my presentation is the use of stated preference methods. While this is an evolving science, the CDRH and the device community have done a lot of work around quantifying patient preferences and tolerance for risk. It also gives the opportunity for those who don't have the luxury of attending meetings like this, or even an advisory committee meeting, participating in certain forums, because they have a day job, and they have a lot of things on their plate. But when you can give them the ability to take a survey using these methods, you can then get and capture the preferences of a much larger group of people and better understand the community's preferences as it relates to benefit and risk. I think we should utilize these tools. We're excited that FDA is going to be coming out with guidance around patient preference information. But in the meantime, I think that for myself, who doesn't have a child living with the condition, I'm a stronger advocate going to a meeting with data in hand and describing what I'm learning about how patients think and feel about benefit and risk of a given therapy.

MS. ROWZEE: Thanks, Ryan. Amanda, Andrew, and Annie — or Jennifer, excuse me — any thoughts to share?

MS. KENNEDY: I think Ryan said it beautifully. I would just offer another resource. Did you know that the NYU School of Ethics has done a lot of work looking at the ethical considerations of families who participate in clinical trials and the patient preferences and benefit/risk considerations, not just around efficacy and safety, which of course are incredibly important, but also around dose escalation and, of course, some of the important differences between participating in therapeutic trials in the drug space versus those in the cell and gene therapy space and the considerations that families make? I might just point to that as a really incredibly important resource. I know that many of us participate in that forum and just would love for that to be on the docket here today. I think this is an incredibly important

question, and I thank you for the question. But there are a lot of very thoughtful bioethics experts who have convened forums with many of the patient community experts here today to really be thoughtful about some of these questions and considerations.

MS. BEEDLE: And I'll just jump on quick, if I may. Thank you, Ryan and Annie, and thank you, Dr. Hart, for that. That's a great question. And as our CLN2 community had first presented, we very well understand the potential of severe risk. But given the situation our community finds ourselves in, it is a situation of death or death regardless, and I'm hopeful in the days ahead, as these processes are looked at and discussed, especially in a sort of a post-COVID paradigm, looking at safety and speed kind of somewhat being paired because of the great need. I think myself and many of us in the rare community are eager to see that process streamlined and looked at in the days ahead. Again, I thank you.

MS. ROWZEE: Okay. I think we might have one final question. Dr. Lapteva, did you have a question?

DR. LARISSA LAPTEVA: Yes, thank you. My name is Larissa Lapteva, and I'm from the Division of Clinical Evaluation and Pharmacology and Toxicology, also here in OTAT. I would like to thank all of the presenters and speakers for sharing your perspectives and feedback and opinions — and not only yours but also your communities'. We try to partner with patients when we work with sponsors who are developing gene therapy products. And my question is kind of for everybody on this panel, and maybe for other participants who spoke during other sessions.

In your conversations with your communities, maybe getting some questionnaires answered or tools developed, what are the most striking, to you, misconceptions that you encountered when talking with patients and caregivers about gene therapy products, about development of gene therapy products, about clinical trial participation? It's important for us to understand the misconceptions that are out there in order to develop better educational tools. And so, for that, I would like to ask everyone to please speak. Thank you.

MS. BEEDLE: I can jump on just really briefly here. Perhaps one misconception I see is just that it needs to be a closed-off process and — even just through meetings like this, and our community is so grateful; our entire rare community is so grateful — it doesn't need to be. Certainly, those connections and those means could be approved upon to extend just past those here today and the speakers here today. It is a collaborative process. And how can this be a springboard to that continual partnership? Thank you.

MS. ROWZEE: Jennifer, I see your hand raised. Do you want to comment?

MS. FARMER: Thank you, and thank you for the question. When we first started serving our patient community to understand what they understood or thought about gene

therapies, I think there was a misalignment in terms of — there was a lot of expectation that these therapies, out of the gate, would be curative, and we had to do a lot of work to educate the community and help people understand what these therapies can do and what they can't do. And I think part of that misconception comes from the unmet need. And in some ways, the hope of even just what the title sounds like.

And several other speakers, I think, have mentioned that earlier today as well. But these are issues that I think our communities are currently have been addressing. And more and more people now do, I think, understand that these are evolving therapies, not necessarily cures. And I think that's where we also heard some of the comments today about needing to consider these therapies along with other therapies as well and how we do that effectively as rare disease communities.

MR. FISCHER: I completely agree with that. We had to do the same around education. I actually get worried about the term “one-and-done.” For many families, they feel “one-and-done” — that this will be it in a progressive rare disease. Often times, we understand that, over time, they're going to need to add on therapies, so it's constant education. But I will also say that therapeutic misconception can begin in a doctor's office. And a physician may not have the same information as one of the leading experts or others within our community. And there's variation with what physicians are telling patients. We have to remember that piece of the puzzle and understand how physicians are communicating the potential benefits and risks to their patients, because it's often a shared decision-making process. Annie?

MS. KENNEDY: I was going to say, I would almost flip the question around just a little bit, because I do want to — many of the patient groups here have done a really beautiful job of talking about the patient education efforts that have been undertaken by patient groups in partnership with the pharmaceutical partners and other federal agency partners. And as one of my colleagues says, we're really in the middle of the beginning, if you will. We're certainly not in the same place we used to be as far as education of the broader patient community around what cell and gene therapy even is, what the risks associated with being a part of cell and gene therapy trials are, what the term “durable therapies” may or may not mean.

And I think one of the things that is sometimes underappreciated by many of us is what families are already risking in order to be even eligible for screening into gene and cell therapy trials. When families and communities are first learning that these trials are starting in their respective disease spaces, many of us now appreciate what it means to be isolated and in our bubbles, coming out of COVID. But there are families who live like that and lived like that pre-COVID in order to try and protect themselves and be eligible for gene and cell therapies and to ensure that their children could be as eligible as possible for gene and cell therapies, long before COVID was commonplace. And people understood what that meant, what risk of

exposure meant, the sacrifices that families undergo in order to even just screen into a trial.

And then I just want to go back to the point around the dosing and the subtherapeutic doses that families receive when they're the first to participate — or potentially subtherapeutic doses families receive if they are the first in a study, versus those that may ultimately benefit from what's commercially available. Patient communities are doing a beautiful job of explaining that and working with partners to explain that, but I just don't want to underestimate the savvy of the patient communities that are understanding what it takes to move therapies forward and the sacrifices that, collectively, communities are undertaking to move therapies forward for their communities. But it is nuanced and it is difficult to communicate. But communities understand, to your first question, the risk of doing nothing is certain and that it is worth risking moving these programs forward.

MS. ROWZEE: Thank you, Annie, and I saw a lot of head nodding going on during your comments.

Once again, just a thank-you to our Session 4 panelists, especially for sticking around and taking our questions.

Again, just a heartfelt, warm thank-you to everyone for attending today's meeting and a very special thank-you to our public speakers for your time and your participation today and sharing your stories and your thoughts in considering these four very important topics.

Just a few reminders. As I mentioned earlier, a recording of today's event will be posted on FDA.gov in the next few weeks. If you have additional comments to share — and I've seen so much, as I said, so much robust discussion going on in the chat box, we really encourage folks: If you have additional comments, please submit them to our docket. We want to make sure that they get captured in the docket. It's going to be open for public comment until December 15. Within 6 months of this meeting, FDA will issue a report summarizing the views expressed today and the comments from the docket. This report will also be available on FDA's website.

Thank you one last time again for joining, for your time today. Have a great day. Take care now.

[END RECORDING]