

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

1

1 U.S. FOOD & DRUG ADMINISTRATION

2

3 INBORN ERRORS OF METABOLISM

4 PATIENT-FOCUSED DRUG DEVELOPMENT

5 PUBLIC HEARING

6

7

8 June 10, 2014

9 9:01 AM - 1:02 PM

10

11 Food and Drug Administration

12 White Oak Campus

13 10903 New Hampshire Avenue

14 Silver Spring, Maryland

15

16

17

18

19

20

21 Reported by: JEN METCALF, RPR/CSR,

22 LDM Reporting

23

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

2

1 A P P E A R A N C E S

2 FDA REPRESENTATIVES:

3 SARA EGGERS, PhD

4 DONNA GRIEBEL, MD

5 THERESA MULLIN, PhD

6 TERESA BURACCHIO, MD

7 PUJITA VAIDYA

8 RONALD FARKAS

9 RACHEL WITTEN

10 JULIE BEITZ

11 JAMES BONA

12 LARRY BAUER

13 PARTICIPANTS:

14 WHITNIE STRAUSS

15 TRACY VanHOUTAN

16 STEVE HOLLAND

17 CHRISTINE BROWN

18 MELISSA HOGAN

19 JENNIFER PAYNE

20 DEAN SUHR

21 ROY ZEIGHAMI

22 MELISSA BELINNI

23

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

3

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

2 PARTICIPANTS:

3 ANDREA SMITH

4 ANDREA FURID-HELMS

5 AUSTIN NOLL

6 JANA MONACO

7 MARY O'DONOVAN

8 EDUARDO BALCELLS

9 LINDA MUUL

10 HOLLON STEVENS

11 PETER COMO

12 JILL WOOD

13 CRISTY BALCELLS

14 RHONDA CONNOLLY

15 GORDON WINGATE

16 GINA WILLIAMS

17 ROSS BENNETT

18 EILEEN LINZER

19 AMYU MILLER

20 AMBER MORGAN

21 UNIDENTIFIED MALE

22 NODIA BODKIN

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

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

2 PARTICIPANTS:

3 BECKY VIVIAN

4 STEPHANIE BOZARTH

5 JOYCE WOLFE

6 LPAIGE MIGLIOZZI

7 WILLIAM NYHAN

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

5

1 C O N T E N T S

2	AGENDA ITEM/SPEAKER:	PAGE
3	Welcome and Opening Remarks	7
4	Sara Eggers, PhD	7
5	<i>Office of Strategic Programs (OSP), Center for</i>	
6	<i>Drug Evaluation and Research, (CDER), FDA</i>	
7	Donna Griebel, MD, Director,	10
8	<i>Division of Gastroenterology and</i>	
9	<i>Inborn Error Products (DGIEP),</i>	
10	<i>CDER, FDA</i>	
11	Background and Context	13
12	Theresa Mullin, PHD	13
13	<i>Medical Officer, DGIEP, CDER, FDA</i>	
14	Teresa Buracchio, MD	21
15	<i>Medical Officer, DGIEP, CDER, FDA</i>	
16	Sara Eggers, PhD, OSP, CDER, FDA	30
17	Panel #1 Comments on Topic 1	43
18	<i>Topic 1: Neurological manifestations of inborn</i>	
19	<i>errors of metabolism that matter most to</i>	
20	<i>patients. A panel of patients and patient</i>	
21	<i>representatives will provide comments to start</i>	
22	<i>the discussion.</i>	

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

6

1 C O N T E N T S (Continued)

2	AGENDA ITEM/SPEAKER:	PAGE
3	Large-Group Facilitated Discussion on Topic 1	69
4	Panel #2 Comments on Topic 2	115
5	<i>Topic 2: Approaches to treating neurological</i>	
6	<i>manifestations of inborn errors of metabolism and</i>	
7	<i>perspectives on informed consent for clinical</i>	
8	<i>trials.</i>	
9	Large-Group Facilitated Discussion on Topic 2	147
10	Open Public Comment	185
11	Closing Remarks	196
12	Teresa Buracchio, MD, CDER, FDA	196
13	Sara Eggers, PhD, OSP, CDER, FDA	291
14		
15		
16		
17		
18		
19		
20		
21		
22		

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

7

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

2 DR. EGGERS: Good morning, everyone. I
3 guess I don't have to tell everyone to take your
4 seats. Usually, I have to give a pretty rowdy crowd a
5 few minutes to get settled but you guys are ready to
6 go, so I think we should get started with this
7 meeting.

8 My name is Sarah Eggers and I'm in the
9 Office of Strategic Programs here at FDA Center for
10 Drug Evaluation and Research. I'm going to let my
11 colleagues introduce themselves in a minute, but I
12 want to welcome you here to an important meeting in
13 inborn errors of metabolism. We have a very engaging
14 discussion ahead and I'll explain the format of that
15 discussion a little bit later on before we get into
16 it.

17 But just a few housekeeping things and
18 agenda items. So on the agenda, we're first going to
19 have our FDA colleagues set the context for why we're
20 here, why this meeting is important, a little bit of
21 background. I'll come back and give an overview of
22 the discussion format before we get into it.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

8

1 This meeting is very different from meetings
2 that FDA or others in regulatory agencies might
3 conduct on this.

4 Then we're going to have two discussion
5 topics today. The first discussion topic will be on
6 the disease symptoms and daily impacts that matter
7 most to patients followed by a discussion after a
8 break on patients' perspective on current treatment
9 approaches to treating inborn errors of metabolism,
10 and this includes things such as participating in
11 clinical trials and your experiences with treatments.

12 There is an open public comment session
13 today and this gives people a chance, not just the
14 patient and the patient representatives in the room,
15 but anyone a chance to contribute a few comments on
16 this topic of IEM or other things you think are
17 important. We'll ask you to sign up at the
18 registration table. If you haven't done so, depending
19 on the number of people who sign up, we'll set the
20 time for that. It will be no more than three minutes
21 and we'll ask you to keep your comments short. We
22 want, really, to engage in the discussion on the two

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

9

1 discussion topics.

2 And then we'll have some closing remarks by
3 my colleague, Teresa Buracchio at the end of this
4 meeting.

5 There are restrooms located around the
6 corner behind that kiosk and keep going down the hall.
7 There is a kiosk here for light refreshments. Please
8 feel free to get up as you need whenever you need.
9 And if you need anything during the meeting, my
10 colleagues are around.

11 This meeting is being recorded. It's on the
12 webcast and I want to give a special welcome to those
13 of you who are attending on the webcast. You will
14 also have every opportunity to participate today
15 through the facilitated discussion, through the -- by
16 submitting your comments. As we ask questions up
17 here, just go ahead and respond to those through the
18 webcast. And the meeting, as it's being recorded, a
19 transcript of this meeting will be posted on our
20 website some days following the meeting.

21 So with that, I'm going to ask my colleague,
22 Do9na Griebel, to come and give some opening remarks.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

10

1 Thank you.

2 DR. GRIEBEL: Good morning, everyone.

3 Welcome to the patient-focused drug development
4 meeting on neurologic manifestations of inborn errors
5 of metabolism. I'm Donna Griebel. I'm the Division
6 Director for the Division of Gastroenterology and
7 Inborn Errors Products in the Office of New Drugs at
8 FDA. Our division reviews drugs intended to treat
9 inborn errors of metabolism, or I'll refer to that as
10 IEM for short.

11 We're happy to see so many patients in the
12 room today and patient advocates in the room, and we
13 understand that you represent a wide range of IEM
14 disorders. And I understand that there are many more
15 patients and advocates on the -- joining us via the
16 web, so welcome, everyone.

17 Today's meeting is one in a series of what
18 we're calling FDA's patient focus development
19 meetings. Dr. Theresa Mullin will be providing more
20 details on this initiative in a few minutes.

21 The inborn errors of metabolism include a
22 range of genetic disorders in which the body has a

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

11

1 metabolic deficiency that results in a buildup of
2 harmful substances in the body. Dr. Teresa Buracchio,
3 who is a Medical Officer in our Division and who is
4 also a specialist in neurology, will provide a bit of
5 background on IEM in a few minutes as well.

6 This is a very important meeting to us. We
7 fully understand that inborn errors of metabolism are
8 serious conditions and that there is an unmet medical
9 need for patients who have these disorders. It's
10 FDA's responsibility to ensure that the benefits of
11 drugs outweigh the risk and, therefore, having this
12 kind of dialogue with you is extremely valuable to us.
13 What we hear from you today can help us understand how
14 patients view benefits and risks for treatments for
15 IEM.

16 We also know that we need better end points
17 to measure how well these drugs are working, and
18 that's why we want to hear from you today about the
19 different ways that neurologic symptoms of IEM affect
20 your daily life and/or your child's daily life. It's
21 also important to hear what you value in a treatment
22 and what you would like to see in future treatment for

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

12

1 you or for your child.

2 Finally, we would like to hear about the
3 considerations that you think are important regarding
4 clinical trial participation as well as the informed
5 consent process.

6 It's important to remember that FDA is just
7 one part of the drug development process. We don't
8 have primary responsibility for developing drugs or
9 for running clinical trials. Drug companies working
10 with investigators, researchers, and the patient
11 community are the ones who conduct the trials and who
12 submit the application for drugs to FDA. However, at
13 FDA, we work closely with drug companies throughout
14 the drug development process. In our Division, we are
15 particularly anxious to work early and often with
16 companies who are developing drugs for rare diseases.
17 And through these meetings, we work together to try to
18 ensure the trial's design will be successful in
19 defining the efficacy and the safety of the drugs in
20 development. Our Division firmly believes that the
21 best access for patients to an effective drug is
22 through the availability of an approved drug.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

13

1 I know there are a lot of representatives
2 from industry, academia and others in the room or
3 joining us via the web. Thank you, all, as well for
4 being here and being part of this discussion. We
5 believe this meeting will provide valuable input for
6 you as well.

7 So again, welcome to everybody. I'll turn
8 the meeting over now to Theresa Mullin who will talk
9 about the broader efforts.

10 DR. MULLIN: Thanks, Donna. Good morning
11 and so as she said, I'm Theresa Mullin. I direct the
12 Office of Strategic Programs in the Center for Drugs,
13 and our office has the privilege of leading this and
14 organizing this initiative and working and supporting
15 our medical officers and our divisions to prepare for
16 these meetings.

17 So just to tell you a little bit about this.
18 We initiated this patient-focused drug development
19 effort as a part of a commitment that we made under
20 the re-authorization of the Prescription Drug User Fee
21 Act, and this is the fifth time around for this so
22 this is a PDUFA V is what we call it. And this

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

14

1 initiative is intended to provide us with a more
2 systematic way to collect information from patients,
3 getting their perspective on serious conditions,
4 conditions for which there may not be very many
5 available, if any available, approved therapies. And
6 we realized we needed a way to do this outside of the
7 context of a particular drug because it allowed us to
8 just get patient input without worrying about
9 screening for conflicts of interest or anything. We'd
10 have a much more free-flowing and rich communication,
11 we though, from patients. We'd hear a lot more if we
12 could just do this independent of any particular drug,
13 and it would inform the development of a wide range of
14 drugs perhaps for that disease.

15 And we knew that the patients would provide
16 us with this unique perspective that no one else can
17 because patients are the ones that are going to get
18 any benefit from a drug, and they'll be experiencing
19 whatever risks are associated with that drug. And so
20 this patient perspective, this unique perspective
21 gives us a better understanding of the context of the
22 disease and the context in which we'll evaluate the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

15

1 benefits versus the risks of a new drug therapy.

2 We thought this kind of input would help us
3 throughout the development process even during early
4 stages of development to weigh benefits and risks as
5 they emerge and as the picture of evidence emerges for
6 a new drug as well as helping us at the time of
7 application review. And so this patient-focused drug
8 development initiative is one in which we commit to do
9 at least 20 different disease areas, and we see this
10 as piloting an approach that we think we really would
11 like to have all disease areas. We'd like to have
12 this kind of patient input to inform every possible
13 disease area. Within our limited resources, we're
14 doing 20 and then some over the next -- over this
15 five-year period, and we're learning a lot about
16 what's effective and what works well.

17 Some patient groups are even approaching us
18 to see if we can't sponsor the meeting, would they
19 sponsor the meeting and we come and we're trying to
20 work that out because we think this is a really
21 important source of input for us.

22 And so which 20 diseases were we going to

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

16

1 cover in this five-year period? So we had a public --
2 we put out a *Federal Register* Notice with about 40
3 disease areas that we identified, the review divisions
4 identified, as ones where they felt we'd really
5 benefit from having some more input. They didn't
6 get -- have a lot of information -- as much as they
7 would like. We got a lot of public comments. For the
8 first three years of the five-year period, we've
9 picked 16 diseases. You know, this topic of
10 neurological manifestations of inborn errors of
11 metabolism was a kind of a cluster and one that was on
12 our list and is on this first three years list. And
13 here you see the diseases that we're focusing on in
14 those first years, 2013 to '15.

15 And so last year we had meetings on chronic
16 fatigue syndrome, HIV, lung cancer, and narcolepsy.
17 And so far this year, we've had a meeting on Sickle
18 cell disease, a meeting on fibromyalgia. Last month
19 we had one on pulmonary arterial hypertension, and
20 this meeting now on inborn errors of metabolism. And
21 on the right side of the slide, you see the ones we
22 have for the remainder of this year and then next year

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

17

1 and soon we'll be coming out with our process to try
2 to identify ones that we'll try to cover in these
3 kinds of formal meetings in 2016 and '17.

4 And as you note, those are -- it's a really
5 wide range of disease areas that we had on that slide,
6 and just to go back for a second, I mean, very wide
7 ranging but have in common that we really would
8 benefit from hearing more about what it's like to live
9 with these diseases, what do patients do today to
10 treat their disease, what kinds of therapy do they try
11 to work with, and so we need that across that wide
12 range.

13 And so we have common themes and questions
14 that we focus on in these meetings even though the
15 diseases that we're looking at across the whole set
16 are quite diverse. And so with each one, we set --
17 start out with a fairly basic set of questions and we
18 use a very similar set of questions each time. We
19 have some tailoring of those questions depending on
20 other questions that the review division may have that
21 they would like to probe and hear from patients about
22 this gives them a unique opportunity to get that kind

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

18

1 of input, so we have those kinds of questions as well.

2 But we start with a set of questions about
3 what it's like to live with the disease, what are the
4 most bothersome, most important impacts on the
5 patient's life from a caregiver's perspective, also
6 from a patient's -- directly from a patient's
7 experience and their perspective if they're able to
8 talk -- to tell us about that. And then also, what
9 are they doing to treat their disease are the two
10 major themes. And these are important aspects of our
11 benefit-risk assessment. Those two questions of the
12 degree to which this is an unmet need and the severity
13 of this condition are two of the -- the two components
14 that set the stage for our clinicians to make -- try
15 to make an assessment of the context and the benefit
16 risk and weigh the evidence of benefit and the safety
17 information in that context.

18 So we further tailor the questions. For an
19 example, we had this meeting on HIV and there is --
20 there was a question the review division had about
21 cure research: How would patients who are doing
22 fairly well on the treatments that are available today

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

19

1 feel about maybe going off treatment and trying a sort
2 of a therapy that would be considered a cure; would
3 they be willing to do that? There are potential
4 benefits but also risks and so it was very helpful to
5 hear their perspective on that question.

6 And so we've learned that patient
7 involvement and participation is not only important,
8 it's what makes these meetings successful or not, so
9 we really are looking forward to hearing your
10 perspective today. We know that it will give us very
11 valuable insight that we don't have right now, that
12 later today we'll have a better -- we'll be much
13 better informed than we are right now.

14 And so each of these meetings produces a
15 voice of the patient report, and we collect the
16 information from the patient testimony that we hear in
17 the room. We get perspectives from the docket that
18 people submit electronically, just statements to the
19 docket. We also will get information from people on
20 the webcast. And those are our three major sources.
21 We pull this together and produce a report that tries
22 to faithfully capture what we are hearing in the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

20

1 patient's words describing how it is to live with
2 their condition and what they think about the current
3 therapies available to them. That report not only
4 helps to communicate to our review staff, both those
5 who are here, those who can't make it here, and we'll
6 be able to use that as a resource. Industry sponsors
7 who are thinking about developing drugs in this area
8 will also find that useful.

9 And we think there's a long-run impact here,
10 too. Some of these meetings have triggered
11 discussions about how can we try to develop measures
12 to better capture the things, these benefits or
13 impacts that patients are telling us about so that if
14 we have a new therapy that might actually affect some
15 of those things we're able to capture that information
16 and capture that evidence more systematically and
17 rigorously in a clinical trial, and we may not be able
18 to do that now. So there is what we call patient-
19 reported outcome tools that are sometimes the
20 discussion that follows these meetings as well and how
21 can we try to develop those.

22 And so with that, I'll turn it over to

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

21

1 Teresa Buracchio to provide you with some background.

2 DR. BURACCHIO: Hi. I'm Teresa Buracchio.

3 I'm a Medical Reviewer with the Division of

4 Gastroenterology and Inborn Errors Products, and I'm

5 going to provide a brief overview inborn errors of

6 metabolism or I'll just say IEM for short and talk a

7 little bit about neurologic symptoms that are commonly

8 seen in these diseases.

9 So the inborn errors of metabolism or IEM

10 are a group of rare genetic disorders that basically

11 cause a block in the metabolic pathway that leaves the

12 body unable to properly break down a substance or

13 synthesize certain substances in the body like amino

14 acids or carbohydrates. These genetic defects

15 typically cause deficiencies of specific enzymes that

16 will convert one substance to another. An example

17 would be the sugar, galactose, to be converted to

18 glucose. These metabolic dysfunctions can lead to

19 progressive and permanent damage. Typically, if it's

20 upstream of the enzyme, it'll cause a buildup of a

21 substance that can reach toxic levels in the body.

22 Downstream of the enzyme, it may deprive the body of

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

22

1 essential substances that are needed to support
2 specific functions in the body. And sometimes it
3 alters other metabolic pathways that we haven't yet
4 identified.

5 There are over 200 known inborn errors of
6 metabolism. Individually, these diseases are quite
7 rare but collectively, they account for a significant
8 disease burden in our population. The IEM disorders
9 vary widely in their symptoms and severity and disease
10 progression, so two patients with the same disease may
11 have a different course of the disease. Many of these
12 diseases are fatal in infancy or childhood or even
13 early adulthood. However, on the other end of the
14 spectrum, some may progress quite slowly and some
15 patients may live to adulthood or the symptoms may not
16 even show up until adulthood and the diagnosis may not
17 be made until that time. So that can be the case in
18 Wilson's disease. So we do see a lot of variety in
19 these diseases.

20 The diagnosis can be difficult because
21 symptoms can be vague and non-specific initially. And
22 in some cases in the childhood diseases, children can

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

23

1 develop normally for a while and then later decline,
2 so there can be a delay in onset of symptoms that are
3 not recognized initially. We hope that new screening
4 technologies will increase the identification of IEM
5 disorders before the symptoms arise, and the hope is
6 that earlier identification will allow for earlier
7 therapeutic interventions to improve morbidity and
8 mortality.

9 So the symptoms or manifestations of IEM
10 vary greatly depending on the underlying disorder.
11 IEM can affect any of the major organ systems in the
12 body, although some of the ones that we see more
13 commonly are changes in physical appearance,
14 involvement of the respiratory or cardiovascular
15 system, involvement of the musculoskeletal system with
16 ether joint contractures or muscular weakness, liver
17 enlargement or dysfunction and very commonly, we see
18 neurological involvement which may include cognitive
19 symptoms, psychological, or behavioral symptoms.

20 The neurological symptoms are particularly
21 common across the range of IEM disorders and are a
22 significant burden for both patients and their

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

24

1 caregivers. These symptoms are important to patients
2 and the FDA recognizes that they have a significant
3 impact on your daily lives, and we felt that it was
4 important to explore these symptoms further so that
5 they can be better accounted for in drug development
6 programs for these diseases.

7 So just to go into depth a little further on
8 what are some neurologic signs and symptoms, when we
9 talk about neurologic symptoms, we often tend to think
10 only of the brain, but I want to remind everyone that
11 the nervous system not only includes the brain but
12 also includes the spinal cord and the peripheral
13 nerves that go out throughout the body to innervate
14 the different organs in the body.

15 Some of the more common symptoms that we might
16 see in IEM diseases are seizures, vision and hearing
17 loss. Cognitive problems are quite common, and this
18 can range in the spectrum from poor attention and
19 concentration to more severe cognitive decline leading
20 to a frank dementia. There can be language delay.
21 We're hearing from many of you that you are seeing
22 behavior problems in your loved ones that can be

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

25

1 similar to those seen Asperger's or autism disorders,
2 things like hyperactivity, impulsivity, compulsive or
3 repetitive behaviors, or sensory processing issues.
4 And we are interested more about those today.

5 And sleep problems can be problems such as
6 apnea or insomnia. Weaknesses are pretty common as
7 well and along with that, there may be problems with
8 swallowing or breathing, spasticity or stiffness in
9 the muscles can be painful. On the other spectrum of
10 that, we can see low muscle tone and hypotonicity.
11 Abnormal movements can occur, things like myoclonic
12 jerks, tremors or dystonia, coordination and
13 clumsiness both in fine motor movements and also in
14 walking with ataxia. And involvement of the
15 peripheral nerves can lead to numbness and tingling
16 and pain. Pain can be neuropathic pain from the
17 nerves or it can be more, you know, diffusely
18 localized in the body depending on the area involved.

19 Bowel or bladder problems can cause a
20 significant problem for caregivers, I know. And
21 again, walking problems or balance problems, either
22 patients never start walking in the first place or

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

26

1 they do reach the point of developing those motor
2 milestones only to decline later.

3 This list is not exhaustive. As I
4 mentioned, the nerves innervate organs throughout the
5 body, so sometimes neurologic symptoms can be vague or
6 difficult to localize. We want to hear about the
7 neurologic symptoms that are important to you and
8 affect your daily lives. And feel free to tell us
9 about any of them, no matter how small. And even if
10 you're unsure of what you're experience even as a
11 neurologic problem, we still want to hear.

12 As far as treatment options, the goal for
13 treatment of IEM disorders is to reduce symptoms,
14 improve quality of life and ideally, slow or halt
15 disease progression. Current therapies are limited.
16 They may include dietary restrictions or dietary
17 supplementation or medical foods. Enzyme replacements
18 are available for a select number of the diseases such
19 as Elaprase or Naglazyme. Bone marrow transplantation
20 may be an option early in the disease for some of the
21 inborn errors of metabolism or organ transplantation
22 later.

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

27

1 Most commonly, though, what we see are
2 supportive therapies, things that treat the symptoms
3 of the IEM disorders but don't necessarily alter the
4 underlying course of the disease, medicines to treat
5 seizures, the use of feeding tubes, ventilators. And
6 we're also hearing from you that many of you make use
7 of behavioral, physical or occupational therapy so we
8 would be interested in hearing a little bit more about
9 those as well today.

10 There are many challenges in developing
11 drugs for IEM disorders. And, of course, the most
12 obvious one is that these are rare diseases so there
13 are a very small number of patients with the disease.
14 PKU is one of the more common ones but, you know, we
15 are seeing applications come in for diseases where
16 there are less than 100 patients identified worldwide.
17 And within these rare diseases, then there are
18 patients with a great deal of heterogeneity or diverse
19 presentations of the disease. As I mentioned before,
20 two patients with the same disease may have very
21 different symptoms.

22 These diseases may occur in both children

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

28

1 and adults which presents another special drug
2 development challenge because children, you know, are
3 vulnerable patients who are not able to consent for
4 themselves. So we have to take special considerations
5 in mind to protect children in pediatric clinical
6 trials that we don't have to consider as thoroughly in
7 adult patients who are able to consent for themselves.

8 And then most of these diseases, again,
9 because they're rare have very poorly described
10 natural histories or descriptions of their clinical
11 progression over time. That makes it difficult for us
12 to identify what endpoints we should be monitoring in
13 clinical trials, what signs and symptoms should we be
14 measuring, and how do we measure them.

15 And if it's a slowly progressive disease, do the
16 disease symptoms progress in a time course that's
17 amenable to a clinical trial which tend to be
18 relatively short? Is the measurement tool that's used
19 applicable to both children and adults? And if
20 biologic disease markers or biomarkers exist, are they
21 even relevant to the disease? So these are all
22 considerations that we have to take in mind as we

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

29

1 review -- as, you know, the pharmaceutical industry is
2 developing the clinical trials and as we're reviewing
3 them.

4 Now in order to help identify better
5 endpoints for clinical trials, the FDA is very
6 interested in patient-reported outcomes. Patient-
7 reported outcomes, or PROs, can represent direct
8 measures of treatment benefit identifying how a
9 patient feels or functions. An example of this might
10 be a pain scale or a scale that measures symptoms of
11 ADHD. For conditions like the IEM disorders that are
12 not well understood, input from patients is especially
13 important. Patient and caregiver input is essential
14 to capture important and clinically relevant disease
15 symptoms in these PROs.

16 And I should also mention that although
17 these are called patient-reported outcomes, in some
18 cases, patients cannot report for themselves if they
19 are too young or too cognitively impaired to give us
20 those descriptions. So in those cases, caregiver-
21 reported outcomes may be appropriate.

22 I should also say that although we do want

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

30

1 this information and we do want these symptoms and we
2 want to see PROs developed, all of these PROs that are
3 developed do still need to be validated and evaluated
4 in adequate and well-controlled randomized trials in
5 order to be used in more pivotal clinical trials for
6 drug development.

7 So today we are here to listen to you.
8 There are representatives here from the pharmaceutical
9 industry, people from the FDA. Please use this
10 opportunity to share with us the neurologic symptoms
11 that are important to you and that impact your daily
12 lives. And, you know, we are interested to start
13 incorporating these into the drug development process.
14 Thank you.

15 DR. EGGERS: Thank you very much to Donna
16 and both Theresa's/Teresa's. I'm going to give a
17 little bit of background of our discussion format but
18 both of you have set it up very nicely, so hopefully,
19 I don't have to spend too much time speaking. We can
20 get right into the discussion.

21 Before we do that, I neglected to have my
22 FDA colleagues introduce themselves. These are the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

31

1 experts, the real experts in the drug development and
2 review of IEM products. So I would like you to go
3 around and just say who you are and what office you're
4 from.

5 DR. FARKAS: Ron Farkas from the Division of
6 Neurology Products.

7 DR. WITTEN: Rachel Witten. I'm from the
8 Office of Cellular Tissue and Gene Therapy.

9 DR. BEITZ: Julie Beitz, Director, Office of
10 Drug Evaluation III.

11 DR. GRIEBEL: I already introduced myself.
12 I'm Donna Griebel from DGIEP.

13 DR. MULLIN: Theresa Mullin. I direct the
14 Office of Strategic Programs in the Center for Drugs.

15 DR. BURACCHIO: Teresa Buracchio, Division
16 of Gastroenterology and Inborn Errors Products.

17 DR. BONA: Jim Bona, the Office of Orphan
18 Products Development.

19 DR. BAUER: Larry Bauer, Office of New
20 Drugs, Rare Disease Program.

21 DR. EGGERS: Thank you very much, and they
22 will be up here to help further the discussion, ask

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

32

1 some more follow-up questions. If you and the -- you
2 as participants say something that really peaks their
3 interest or they want to follow-up on that, they are
4 free to do so.

5 As we've mentioned, the two topics are the
6 neurological manifestations of IEM, that means the
7 effects, the neurologically-related effects of IEM
8 that matter most to your child or your, if you're the
9 patient's, life. Here we're looking for concrete
10 things. What particular symptoms have the most
11 significant impact on that daily life? How do they
12 affect the ability to do specific activities and how
13 do they change over time?

14 And then we'll move into the current
15 approaches to treating IEM. What are you doing to
16 treat or manage your or your child's IEM; and how well
17 are these addressing those neurological effects; and
18 how do you know that? How do you see, what
19 differences do you see? What are their biggest
20 downsides? And what would you look for in ideal
21 treatment to better serve those needs related to the
22 neurological effects? And then we'll move into a

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

33

1 discussion on clinical trial participation informed
2 consent.

3 For each of those two topics, we're first
4 going to here from a panel of patient representatives
5 typically. We do have one adult patient who will
6 serve on the panel, but primarily your parents who are
7 speaking on behalf of your child or children. These
8 participants reflect a range of experiences with IEM,
9 a range of disorders, and a range of symptoms that you
10 wrote in about or treatment that you have experience
11 with or thoughts you have on clinical trials.

12 And I just want to say thank you to everyone
13 who submitted comments as part of the selection
14 process for the panel participation. Those comments
15 really are helpful to us as we plan for these meetings
16 and understand what you might want to talk about and
17 what's important, what effects are important to talk
18 about.

19 After we hear the panel discussions which
20 really will set up a good foundation for our
21 facilitated discussion that follows, and this we will
22 broaden to include all of you, patients, caretakers,

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

34

1 advocates, and the audience to build on the
2 experiences we heard in the -- by the panelists. So
3 we're going to ask questions talk show style and we
4 invite you to raise your hand to respond. We'll ask
5 you at least say your first name and the IEM disorder
6 that you're talking about. That really sets a context
7 so we know we can put -- we can have the disorder in
8 the back.

9 With that said, we're not going to be
10 focusing on specific disorders. We're not going to
11 run through a list or anything like that. We're
12 focusing on neurological symptoms that are -- that you
13 experience that we can kind of draw generalizable
14 (sic) learnings from across all the different disease
15 areas.

16 I'm going to ask the panelists now, for
17 those that are talking in Topic 1, to come on forward
18 and make your way up to the front table. You also,
19 here in the room and on the web, have a chance to
20 answer polling questions and I'm going to ask the
21 little clickers to be handed out to everyone. So if
22 you're a patient or patient representative, please

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

35

1 raise your hand.

2 The purpose of these questions is to really
3 aid our discussion. They're in no way a scientific
4 survey. They're completely voluntary. You don't have
5 to answer the question. What they do is give us a
6 sense of who's represented, what the representation is
7 in the room and on the web and an indication of what
8 perspectives you might share in common and where they
9 might be differences. Web participants, you'll see
10 the questions in the webcast. We're asking that
11 patients and patient representatives only please
12 answer, and at a certain point, we're just going to
13 ask either the patient themselves or one caretaker
14 answer the question on behalf of that patient.

15 You have to -- these clickers are -- they're
16 not too technologically challenging we hope, but you
17 do have to push the button very deliberately, very
18 hard in order for it to show up.

19 Web participants, as we mentioned, you can
20 add comments through the webcast. Although they won't
21 all be read or summarized today, your comments are
22 incorporated into our summary report and we do read

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

36

1 them all. We'll occasionally go to the phones to give
2 you another opportunity to contribute and there will
3 be information on the webcast at the appropriate time.

4 You can also send us your comments through
5 the public docket. This is a website that federal
6 agencies have that we can receive comments from the
7 public on topics that are important to us, topics that
8 we open a docket for. We have one open for
9 neurological manifestations of IEM. It's open until
10 August 11th, 2014, and we really encourage you if
11 you're here in person or on the web to expand upon
12 what you said here or to share your fuller story
13 through the docket. And if you know people who
14 weren't able to make it today, encourage them to share
15 as well. The more information we get, the more
16 valuable it all is. Anyone is welcome to comment. It
17 can be healthcare providers, researchers, industry,
18 anyone.

19 A few ground rules to make sure this
20 discussion is as effective as possible. We really do
21 encourage patients, caregivers, and advocates to
22 contribute to the dialogue. Industry, researchers and

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

37

1 others, we very much appreciate you being here. We
2 ask that you be in listening mode throughout the
3 discussion. If you'd like to contribute, there is the
4 open public comment.

5 My FDA colleagues are here to listen. They
6 might not be able to answer all of the questions that
7 you may have. If you do have questions for us and
8 they can't be answered today, please either send us --
9 there's a patient-focused email that you've been
10 getting correspondence on. Send us an email with that
11 or submit a larger comment, a more -- a comment you
12 just want us -- a question you want us to think about
13 through the docket. We will consider it then.

14 The discussion will focus on those symptoms
15 and treatment and as Teresa Buracchio, it's very hard
16 to sometimes tell if it's a neurological symptom. We
17 don't want you to worry about that. If it's important
18 to you and you think it might be neurologically-
19 related, please share it. Same with treatments -- we
20 don't want to focus on particular treatments. This
21 isn't here to really evaluate your experience with any
22 specific treatments. What we're doing, again, is

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

38

1 looking to see what can we learn broadly about these
2 treatment and their development that we can continue
3 to help improve that. If you -- again, if you have
4 other comments on other topics, please feel free to
5 use the open public comment period, sign up for it
6 outside on the registration table at the break. Sign
7 up by the break so that we know -- we have that set.

8 Of course, the views expressed here today
9 are personal opinions, and we truly know there is a
10 range of your experiences, a range of severity, a
11 range of the difficulties and the challenges you face.
12 But everyone here today who is a patient or patient
13 representative or an advocate is fully aware of these
14 challenges in your own life. You experience them and
15 you know others who do. So we feel -- please feel
16 free to share your experiences in a comfortable
17 setting. We're all here to listen. With that,
18 respect for one another is paramount. That goes
19 without saying.

20 And please let us know how we're doing, how
21 the meeting went well -- how the meeting went today.
22 We hope it went well. The evaluations will be at the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

39

1 registration desk.

2 So with that, we will start with a few
3 polling questions just to get our fingers warmed up
4 and to test these things out. If you're on the web,
5 there are polling questions as well. First one is
6 where do you live -- and everyone with a clicker can
7 feel free to answer this question -- within the
8 Washington, DC area, including the suburbs, or outside
9 of the Washington, DC area?

10 (Whereupon, in response to polling, the
11 results are as follows: within DC, 17%;
12 outside DC, 83%.)

13 DR. EGGERS: Okay. AS we expected, most of
14 you live from outside of the area. We think all of
15 you have traveled here today to be with us and to
16 share your comments whether you just had to come
17 around the beltway or whether you had to travel more
18 extensively.

19 Have you or your loved one ever been
20 diagnosed as having an inborn errors of metabolism?

21 (Whereupon, in response to polling, the
22 results are as follows: yes, 87%; no, 13%.)

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

40

1 DR. EGGERS: Yes. So it looks like if I
2 have to do some math calculations in real time, more
3 than 25 of you here are representing patient or you're
4 here for yourself representing them. That is great to
5 hear. We very much value your experience.

6 I'm going to ask that the rest of the
7 questions just be answered by either the person who
8 lives with the IEM themselves or one caretaker just so
9 that we don't over-represent any particular
10 individuals.

11 What is your or your loved ones age? We
12 understand that many of you have multiple children, so
13 hopefully they fit in the range or think of one child,
14 0 to 2; 3 to 9; 10 to 17, you'll press "C"; 18 to 35,
15 34 to 49; 50 or greater or your loved one has passed.

16 (Whereupon, in response to polling, the
17 results are as follows: 0-2, 0%; 3-9, 38%;
18 10-17, 17%; 18-35, 25%; 34-49, 8%; 50 or
19 greater, 0%; deceased, 13%.)

20 DR. EGGERS: We do have a wide range and
21 that's very helpful for us. Many, many -- well,
22 actually, we have no one here in the infantile range.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

41

1 On the web, can we have those numbers as well?

2 (Whereupon, brief pause waiting for polled
3 responses.)

4 DR. FURID-HELMS: So a lot of them -- 33
5 percent 3 to 9; 25 percent, 10 to 17; and 23 percent,
6 18 to 34.

7 DR. EGGERS: Okay. All right. So those of
8 you in the -- with children or anyone, you can, of
9 course, think back to that infantile stage, the young
10 adults -- or I'm sorry, the young infants, but we do
11 have a very nice spread otherwise. Yes, go ahead.

12 AMBER MORGAN: (Off mic).

13 DR. EGGERS: Okay. So did anyone else have
14 a 0 to 2 and they pushed that "a" button and it didn't
15 work? Okay. Keep us informed of those, too. We do
16 get sometimes where these clickers aren't the most
17 reliable. Again, they're not used for any scientific
18 purposes so don't worry about that, but thank you,
19 Amber. We'll call on you.

20 Okay. Is you or your loved one male or
21 females?

22 (Whereupon, in response to polling, the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

42

1 results are as follows: male, 44 percent;
2 female, 56 percent.)

3 DR. EGGERS: Okay. So we have a roughly
4 equal split. Is it the same on the web, similar on
5 the web?

6 DR. VAIDYA: Similar on the web.

7 DR. EGGERS: All right. With that, let's
8 get into the discussion Topic 1. We have five people
9 who will comments. I've put their names up here along
10 with the disorder that they have. I will mention I am
11 not a medical expert. That's why we look for our
12 colleagues to help with these questions, and that
13 includes being able to pronounce most of disease
14 areas, so we will be sticking to the acronyms.

15 So we have a range of the disease areas
16 represented. We have one person who will -- who had a
17 family emergency over the weekend and was unable to
18 attend, so we will dial her in by phone at the right
19 time. And one person, a very dedicated father, took
20 the 6 a.m. flight this morning out of Chicago. He
21 will be joining us when he arrives. I've asked them
22 each to prepare about three to four minutes of

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

43

1 comments, so they're going to go through. And we will
2 start with Whitney. Just push the little button and
3 the microphone will come on. And keep it very close
4 to your mouth. We have a hard time hearing.

5 WHITNIE STRAUSS: Okay. Is this alright?
6 Okay. Yeah, so I'm the mother of a 4-year-old child
7 with CTD. My soon, Reid, has developmental and
8 language delays, retardation, epilepsy. The disease
9 directly Reid's brain function but it's not a
10 progressive disease. So it's likely that Reid will
11 live into adulthood, and it's certain he's going to
12 have a lifetime of constant care.

13 While each day we deal with the obvious
14 hurdles, like Reid's inability to speak or perform the
15 simplest of task, it's really the secondary sensory,
16 behavioral, and cognitive symptoms that seem to most
17 impact Reid's daily stresses and struggles. Reid's
18 sensory issues play an important role in his life.
19 Strong oral aversions and intolerance of many foods
20 limit his diet. It's a constant battle to encourage
21 eating and a financial strain to keep stocked with his
22 rotation of preferred foods. As a result, Reid

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

1 struggles with grow and weight gain, is frequently
2 ill, and is extremely irritable.

3 As he's grown, Reid's clothing and textural
4 intolerances have required us to shift our focus. The
5 4-year-old Reid is now physically able to disrobe and
6 he does. His preference for nudity makes it very
7 difficult to keep clothes, diapers, and shoes on him
8 and we've really had to integrate some adaptive
9 devices in attempts to keep him clothed in public.
10 This battle is ongoing.

11 Aggressive behaviors are also part of Reid's
12 life. Hair pulling, biting, self-injurious behaviors
13 and throwing objects happen all the time at our house.
14 Curtain rods are pulled out of walls, furniture is
15 turned on end, and home decor becomes broken or
16 obsolete. As Reid has matured, we've seen an increase
17 in these aggressive and destructive tendencies.
18 Unable to manipulate toys appropriately means those
19 toys go airborne and injuries happen. Pulling
20 glassware off counters, spilling drinks, breaking
21 household objects, slamming doors and pulling things
22 out of the refrigerator are his common go to tactics

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

45

1 for that immediate attention.

2 Sibling rivalries have emerged and without
3 any speech, Reid's natural defense is to scream, bite,
4 or pull hair. When he's upset, Reid's now biting
5 himself. This leaves to bruising and broken skin but
6 he just continues to use it as an outlet for his
7 frustrations.

8 As the parent of a special needs child, I
9 fear for my son's safety. Severe cognitive
10 impairments leave Reid without any recognition of safe
11 and unsafe and he won't hesitate to run into a busy
12 street, walk out the front door, jump on my dining
13 table, or walk right into a swimming pool. As his
14 fine and gross motor development improves, we're
15 really forced to address these safety issues head on.
16 While he's now equipped with the ability to climb,
17 open doors and run, he's still cognitively unaware of
18 the dangers involved. Reid does not respond to
19 commands such as "no," "stop" or "come," so we're
20 always on guard. We're discovering locks on doors
21 just aren't enough.

22 Despite suffering from endless effects of

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

46

1 his condition, it's the sensory, behavioral and
2 cognitive issues that hold the most power. Leaving
3 the house, whether to go to school, a restaurant, or
4 the grocery store requires forethought and intense
5 preparation. To do these things means that Reid must
6 tolerate clothing, follow basic comments, and then
7 behave in appropriate manners. Screaming and breath-
8 holding tantrums, refusal to wear clothing and being
9 downright uncooperative are the usual deterrents from
10 even attempting these social activities.

11 These symptoms impact Reid directly but they
12 do take a toll on the entire family. As a mother and
13 a caretaker, I find myself forced to choose. How do
14 you cheer on one son from the bleachers while there
15 other is running naked toward the parking lot? While
16 I have a strong need to support one child, I'm forced
17 to adapt our lives to integrate the other.

18 I have many wishes for my son. It's so easy
19 to wish but that just won't change Reid. There is no
20 approved care or treatment right now. The reality of
21 Reid's disease touches every facet of his life and
22 ours. And sure, I would love to hear Reid say "momma"

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

47

1 or stop taking his seizure medicines, but if Reid
2 would just tolerate clothing, if he would just eat
3 something besides donuts and pepperonis, now that
4 would be a significant improvement in his quality of
5 life. The little wins would be the less screaming,
6 the less throwing, biting, tantrums and more engaged
7 and responsive behaviors. The little wins would inch
8 Reid that much closer to a more manageable life, even
9 if that life does require constant care.

10 (Pictures of Reid on slide)

11 DR. EGGERS: Thank you very much, Whitnie.
12 And now we have Christine.

13 CHRISTINE BROWN: As the parent of two
14 children with PKU and as the Executive Director of the
15 National PKU Alliance, the neurological implications
16 of PKU affect the daily lives of my children and lives
17 of adults and families across the U.S.

18 (Slides with pictures of boys.)

19 CHRISTINE BROWN: So my two children with
20 PKU are Connor and Kellen and in this picture, they're
21 standing in front of the tandem mass spectrometer
22 which is the newborn screening test. So that's the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

48

1 machine that reads those results.

2 So as you know, many see PKU as a success
3 story of newborn screening. We've been screening for
4 PKU for more than 50 years in this country. We've
5 been treating PKU for more than 50 years. However,
6 PKU is not solved. We're not done with it. People
7 thought that you just could put these kids on a
8 special diet, they would be fine. However, we now
9 know that this is not the case.

10 PKU is also different from many other
11 different inborn errors in that we are not just a
12 pediatric disorder. We estimate that there are about
13 5,000 adults with PKU in the United States. Some of
14 them are doing quite well. I know adults that are
15 doctors, dieticians, lawyers and executives. However,
16 many are not doing so well. They find it difficult to
17 hold down jobs, have anxiety, cannot handle social
18 situations, and suffer from phobias.

19 Certainly, we are very luck in that PKU is
20 diagnosed and treated from birth and that that
21 treatment can mitigate the most serious consequences
22 of the disease. Our children no longer grow up to be

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

49

1 mentally disabled. However, many have deficits in
2 executive function, information processing, and suffer
3 from depression and anxiety. For example, my son,
4 Connor, was diagnosed with ADHD at the age of five.
5 Research actually shows that 35 percent of all
6 children and adults with PKU have ADHD. However, the
7 rate in the general population is about 7 to 8
8 percent. Researchers don't know exactly why this
9 happens.

10 We don't know much about PKU as we thought
11 we did even 10 years ago. We just don't understand
12 what happens when an excess phenylalanine crosses that
13 blood-brain barrier. PKU is still not solved and many
14 face and struggle with neurologic consequences. It's
15 also difficult for many in our community to control
16 their blood phe levels within the recommended range of
17 2 to 6 milligrams per deciliter.

18 For Connor, my PKU-er that also has ADHD,
19 his symptoms of ADHD dramatically increase even when
20 his blood phe levels are slightly elevated. For
21 example, last year for about four months, his blood
22 phe levels were running in about the 7 to 8 milligrams

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

50

1 per deciliter. This is only 1 or 2 deciliters above
2 the recommended range. However, during this time, he
3 could no longer focus at school. He skipped problems
4 on tests. He had difficulty completing simple
5 assignments and could not follow directions that were
6 more than one step. He couldn't even fill out his
7 sticker chart at school to reward good behavior. He
8 went from being a bright and inquisitive model student
9 to one that was beginning to fail second grade, and
10 his teachers talked to us about holding him back.

11 Connor's struggles are not alone. Current
12 dietary treatment for PKU is difficult to maintain.
13 Many in our community do not have insurance coverage
14 for medical foods. My son, Connor, is easily
15 disorganized, forgets the task he is trying to
16 complete, and has difficulty staying on task. My 6-
17 year-old, Kellen, doesn't display these signs to the
18 extent as Connor, but I do see that his brain takes
19 longer to process information than my other older son
20 who does not have PKU.

21 And here's the challenge. Here's the catch
22 with PKU. To control your phe levels, to be on diet

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

51

1 with medical foods, you have to be very organized and
2 meticulous. You have to weigh and calculate the
3 amount of phenylalanine in every single bit of food
4 you take. You have to record all of this in a
5 journal. Then you have to remember to prepare your
6 formula, use a gram scale, remember to take that
7 formula at least three times a day and possibly take
8 other medication. However, as you're phe levels rise,
9 you're ability to track your treatment and the
10 executive function skills that you need to stay on
11 treatment decrease and so you fail.

12 While I feel extremely blessed that my
13 children with PKU have a treatment, that they are not
14 mentally impaired, that they can go to school, they
15 can go to college, they can have a family someday,
16 they do struggle with executive function. I only want
17 what every parent wants for their children. I want
18 them to have the best outcomes possible and the best
19 opportunities available to them. I especially worry
20 about Connor and Kellen and how they will manage PKU
21 on their own as they grow into young man.

22 DR. EGGERS: Thank you so much, Christine.

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

52

1 Now we have Steve.

2 STEVE HOLLAND: Hi, everyone. In addition
3 to being a dad of three MPS I individuals, I'm also
4 president of National MPS Society. The
5 mucopolysaccharidoses or MPS for short are a family of
6 12 individual syndromes each missing a different
7 enzyme that fall within the broader lysosomal storage
8 disorders.

9 (Slides of pictures of girls)

10 STEVE HOLLAND: They're all progressive,
11 degenerative and terminal. The vast majority of the
12 syndromes are characterized by drastic neurological
13 manifestations including profound cognitive regression
14 and mental retardation. Children with MPS are not
15 typically identified at birth but start to be
16 identified once they start missing developmental
17 milestones. Children begin developing normally
18 gaining skills such as speech and possibly toilet
19 training.

20 However, such skills are eventually lost
21 over time in most of the children and are replaced
22 with extreme restless, overactive and difficult

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

53

1 behavior including not sleeping for days and seizures.

2 As the disease ravages the brain, most
3 children start slowing down, lose the ability to walk
4 or communicate and eventually pass away as their
5 bodies' essential systems shut down.

6 Within the 12 syndromes, there can be
7 extreme variability in the neurologic symptoms with
8 the majority of kids having a severe clinical
9 presentation, as I previously described, while others
10 present with attenuated symptoms like my children. My
11 three children have an attenuated form of MPS I called
12 Hurler-Scheie syndrome. They were diagnosed 20 years
13 ago. Spencer passed away 6 years ago at the age of 18
14 due to a medical accident. Maddie is currently 24-
15 years-old and Laynie is 22-years-old and they both
16 live at home with us.

17 Growing up, their neurologic symptoms were
18 milder than most MPS children but included decreased
19 memory and concentration and learning difficulties in
20 school, especially extremely poor math skills. While
21 they were mostly in regular classes in school, they
22 were in special education for math and English as

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

1 their IQs dropped over time. As opposed to the
2 extremely impaired, they understand that they have
3 cognitive limitations that makes it difficult for them
4 to consider normal activities such as driving a car,
5 going to college, having close friends, getting a
6 normal job or ever living alone. My children have
7 benefitted physically from well over 10 years of
8 enzyme replacement therapy allowing them to live
9 longer, healthier lives.

10 However, it has not helped them
11 neurologically. As a result, Maddie is now suffering
12 from extreme psychiatric symptoms that were previously
13 only seen in the most attenuated form of MPS I known
14 as Scheie syndrome. I believe this is a problem that
15 will continue as the Hurler-Scheie children begin to
16 longer lives. She's developed what is being called
17 bipolar disorder in her teenage years. It is likely a
18 result of the GAG accumulation in a particular area of
19 her brain. It presents itself as mania, depression
20 and psychosis. While it was more or less controlled
21 with medication for approximately five years, the
22 psychosis has been back again continuously for the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

55

1 past nine months. She has been hospitalized with her
2 symptoms but normal psychiatric meds have been unable
3 to control it.

4 Out of the past 24 months, she has been in a
5 psychosis or this altered mental state for all but 7
6 of those months. She is extremely delusional with
7 auditory and tactile hallucinations that constantly
8 taunt her. The voices make her sob daily telling her
9 bad things have happened or will happen. Her quality
10 of life has suffered tremendously from her disease
11 such that she cannot do anything productive including
12 being happy or content for more than a few hours at a
13 time or care for herself and at 22 years of age,
14 cannot be left alone.

15 The neurologic impact on MPS diseases is
16 severe and dramatic. While we currently have approved
17 therapies that help the physical effects of some of
18 our diseases, we have no approved therapies that treat
19 the neurologic symptoms, and we need them, and we need
20 them now.

21 DR. EGGERS: Thank you very much, Steve.
22 And now we have Melissa who will be on the phone, and

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

56

1 I'm going to put a picture -- oh, operator, can we
2 have Melissa join, please? AS I mentioned, Melissa
3 faced a family emergency over the weekend and was not
4 able to attend in person.

5 MELISSA BELINNI: Can you hear me?

6 DR. EGGERS: Hi, Melissa. We can hear you
7 well.

8 MELISSA BELINNI: Okay, good. I just wanted
9 to make sure.

10 DR. EGGERS: Can I get --

11 MELISSA BELINNI: Thank you very much for
12 allowing come to call in, and I really appreciate this
13 opportunity to speak about our Olivia and the
14 neurological effects on our family for Gaucher's
15 disease. She has type 2 or 3. There are three types.
16 Type 1 is non-neurological and there is enzyme
17 replacement therapy that works well for that. Our
18 type 2/3 children do receive enzyme replacement
19 therapy but that's only just to help, you know, the
20 systemic parts of the disease process.

21 Many of the signs and symptoms of the
22 neurological part such as swallowing abilities and

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

57

1 many neurological things -- Olivia experienced
2 laryngeal spasms, myoclonic jerks, seizures, and
3 spasms, increased tone which that's spasticity that
4 Teresa touched on earlier, central apnea. These have
5 been the most significant impact on Olivia's life.

6 Most or nearly all of the babies diagnosed
7 with Gaucher's 2 or 3 have suffered from these blue
8 episodes, but we call them laryngeal spasms. The
9 child's larynx will clamp shut not allowing air to
10 come in or out. As the disease progresses, so will
11 the frequency of these spasms, and many children
12 either succumb to the symptoms so you will not see
13 them live past two or they undergo a tracheotomy. We
14 would have lost Olivia had we not trached her at age
15 one.

16 The myoclonic jerks or seizures and spasms
17 increase with the disease progression as well and were
18 best controlled by a combination of medications. Due
19 to the metabolic nature of the disease, however, those
20 medications will need to be frequently increased and
21 changed often to catch up to the neurological
22 symptoms. Many of these spasms would cause breath-

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

58

1 holding spells so even on a ventilator, as Olivia's
2 disease progressed, she would still turn blue. We
3 always had an Ambu bag ready nearby.

4 Increased tone is also difficult as it
5 created pain and she was never able to sit up or crawl
6 or roll over. So even with physical therapy, the tone
7 was difficult to break.

8 As the disease progressed, my daughter was
9 unable to do most activities that any normal infant or
10 toddler could do. She was unable to walk, sit, talk,
11 sit up, crawl, play with toys unassisted, etcetera.
12 She gained a few milestones in her first five months.
13 She was only able to scoot in a walker which happened
14 to be backwards because her tone put her that way.
15 And, you know, she was only able to do that until
16 about 16 months, but it became difficult for her to
17 hold her head up due to the multitude of anti-seizure
18 and anti-tone and anti-anxiety medications she was on.

19 By 18 months, she was pretty much laying
20 down all the time. She did have the ability to
21 transfer a toy from one hand to the other but
22 eventually lost that ability. She was able to reach

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

59

1 for toys for a while as well but in the end, you can
2 only see just a small effort being made on her part
3 but she couldn't quite get there. We would sit her
4 up, play games, take her outside as you can see in the
5 picture. We would read books to her, play with toys
6 hand-over-hand. She did smile and laughed at silly
7 things. She watched her favorite show. She said a
8 couple of words, only one syllable though. As you can
9 see, she just passed away at the age of three.

10 Over time, as the disease progressed, so did
11 her neurological signs. When she was born, she only
12 had very small movement of her eyes and eventually,
13 she lost her ability to gaze side-to-side or up or
14 down. I think she was able to gaze downward but that
15 was about it. Any other effort to see required to
16 lift up her head which eventually she -- it was really
17 difficult for her to do that.

18 Her eyeballs have developed apraxia and
19 strabismus and her spasms increased over time.
20 (Inaudible) movements came and went depending on how
21 much medication she was on. Myoclonic jerks increased
22 and seizures developed, and these are very difficult

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

60

1 to treat.

2 Towards the end, she would sleep most of the
3 time. Comfort care, palliative care became her number
4 one as we became closer and closer to the day she left
5 us. Towards the end, she lost the ability to urinate
6 on her own whether or not that was neurological or
7 just her body shutting down but it was a difficult
8 time.

9 Other neurological symptoms that many of the
10 children face, including Olivia, are the essential
11 apnea, so she started breath-holding in her sleep and
12 then eventually it would progress farther. So she
13 started with her ventilator only during naps and sleep
14 time and then eventually became 24/7. She also did
15 require a G-tube to eat as well.

16 So as you can see, all of these neurological
17 progressions are extremely difficult and extremely
18 taxing and eventually took her life at the age of
19 three. We were very lucky to have her until three.
20 Many of the Gaucher's 2 children do not live past two.
21 And thank you very much.

22 DR. EGGERS: Thank you so much, Melissa.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

61

1 Melissa -- can she stay on the line? Yeah. Melissa
2 will stay on the line if we, at some point, have an
3 follow-up questions for her.

4 MELISSA BELINNI: Okay.

5 DR. EGGERS: Thank you, Melissa. And
6 finally, we have Tracy.

7 TRACY VanHOUTAN: Good morning. My name is
8 Tracy VanHoutan. I'm founder of the Noah's Hope
9 Batten Disease Research Fund and Board Member of the
10 Batten Disease Support and Research Association, the
11 largest organization in the world dedicated to support
12 a family and scientific research into a group of
13 diseases commonly known as Batten disease.

14 I'd like to thank the organizers at the FDA
15 for their thoughtfulness in putting together these
16 meetings, and including these groups, in inborn errors
17 of metabolism meeting.

18 Two of my three children have a
19 neurodegenerative lysosomal storage disorder called
20 late infantile neuronal steroid lipofuscinosis, more
21 commonly known as late infantile Batten disease. Over
22 time, due to the severe brain atrophy caused by waste

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

62

1 buildup in the brain, affected children suffer mental
2 impairment, worsening seizures, progressive loss of
3 sight and motor skills. And eventually, children with
4 Batten disease become blind, bedridden, tube fed,
5 unable to communicate. Presently, it is always fatal,
6 usually between the ages of 8 and 12. My daughter
7 Laine is currently 8 and my son Noah is 10.

8 To pick just a few of the symptoms is
9 difficult because my children have experienced losing
10 everything, and I truly mean everything. They started
11 life as happy, normal kids. They ran and played,
12 talked just like normal kids, read books, had many
13 friends and playmates, and hit all of their milestones
14 appropriately.

15 But all that began to change at about age 3-
16 1/2 when the seizures and some other symptoms began.
17 I want to speak on a few of these symptoms, first
18 being seizures. This is the symptom that has been
19 with us the longest amount of time. Because of the
20 progressive nature of Batten disease, we continue to
21 adjust the anti-seizure meds. We never decrease meds
22 and often add new medications on top of old as my

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

63

1 children reached the safety limits of their old ones.

2 As many of you know, these anti-seizure meds
3 have serious sedating and other side effects.

4 Sometimes we're not sure if the children have lost
5 abilities due to the disease or because of the many
6 side effects of these drugs. And as many parents in
7 the room here know, your child having a seizure
8 exhausts their small bodies, adds damage to their
9 brains and leaves us as parents feeling helpless and
10 terrified.

11 Another symptom is loss of sight. People
12 who have seizures often report not remembering the
13 seizure episode, but when you're talking about the
14 symptom of losing your sight, it's an entirely
15 different matter. Noah and Laine were and are scared
16 of the darkness that surrounds them. Noah had lost
17 his ability to speak when he world went dark but Laine
18 was still verbal as her sight gradually disappeared
19 and she was terrified and would often cry to us asking
20 us if she would become like Noah.

21 The third symptom I'm going to speak about
22 is -- encompasses a few different things, being loss

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

1 of all motor function. It's a broad category and
2 affects every part of our lives and the lives of our
3 children. Ataxia was one of the early symptoms and
4 led us as parents to restrict the last remaining
5 freedoms our children had. Physical and occupational
6 therapy, padded helmets and adding padding to other
7 items in the home only did so much. Our children's
8 frustration was apparent as they continued to lose
9 motor function. Eventually, both Noah and Laine
10 became totally immobile and wheelchair bound. This
11 has affected us greatly as parents.

12 We had to sell our home to find one that was
13 more accessible for the children and a growing list of
14 equipment, the toll of continued lifting and carrying
15 of Noah and Laine, including bathing, has taken its
16 tolls on our bodies, on my wife and I, and we are now
17 regulars at our local chiropractor and physical
18 therapy clinics.

19 In addition to this, they lost the ability
20 to speak. This, too, has been devastating to the
21 children and us as parents. As our children lost the
22 ability to tell us their wants and needs, we could

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

65

1 sense their constant frustration. I suppose the best
2 way to describe these waning months of their speech,
3 it was sort of like -- they would have a stuttered
4 sentence that they were never able to complete. We
5 would see Noah and Laine try so very hard to tell us
6 something but they were never able to fully
7 communicate with us. The countless hours of speech
8 therapy perhaps only extended their abilities a few
9 months. I would also say that emotionally, this took
10 one of the largest tolls on us as parents, not being
11 able to hear your child's precious voice is truly
12 devastating and something we miss terribly.

13 They have also lost control of their bowels
14 and bladders which necessitates our children still
15 being diapered. Their inability to clear oral
16 secretion requires round the clock suctioning to
17 prevent our children from drowning on their own saliva
18 secretions.

19 Noah and Laine have also lost the ability to
20 eat. Making the decision to take oral foods from your
21 child that they once loved, because of the choking
22 hazard -- because the choking hazard is simply too

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

66

1 high, is something no parent should have to do. We
2 would spend hours carefully feeding the children but
3 eventually had to have a G-tube placed for safety and
4 because Noah and Laine were losing too much weight.

5 As far as activities that are important to
6 our children, I think this was pretty much covered in
7 some of -- my first answer. Children affected by
8 Batten disease lose everything, but here is a list of
9 the some of the things that Noah and Laine used to
10 like to do but cannot do any longer. Noah loved to
11 play baseball and soccer but he can no longer see the
12 ball, run or kick the soccer ball or even hold a bat.
13 Noah used to have a fascination with trains. He loved
14 to watch movies about trains. His favorite park had
15 trains pass by every 20 minutes, and he loved playing
16 with toy trains. All of this is now lost. Noah loved
17 to play with his fraternal sisters, Laine and Emily.
18 I guess the only saving grace here is that Noah never
19 had to experience his siblings losing all of their
20 abilities. Laine had to experience this with Noah,
21 and Emily, Laine's unaffected twin, has had to watch
22 both her brother and sister drift further and further

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

67

1 away.

2 Laine loved to dance on the ballet floor
3 with her sister and classmates. We allowed her to
4 continue doing this as long as we could but
5 eventually, it became too great a danger for her to
6 continue. Laine was also a natural swimmer, loved the
7 pool, the beach, any water she could find including
8 the kitchen sink. We actually delayed having Laine's
9 G-tube put in against our doctor's orders because
10 she -- we wanted her to enjoy the last few months of
11 summer swimming at the pool as we knew it would be her
12 last summer of swimming independently.

13 When talking about how the symptoms have
14 changed over time, all of our children's symptoms have
15 changed so incrementally, you would not really notice
16 from day to day as abilities were lost. It's only
17 really when looking from month to month or quarter to
18 quarter that the losses become real and very, very
19 noticeable. In the beginning, it was few
20 mispronounced words or mixed up sentence structure.
21 Now, in the end, it's silence. In the beginning,
22 there were some mile squinting while looking at books

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

68

1 or watching a movie. Now darkness. And in the
2 beginning, a few clumsy stumbles, some scraped knees
3 and a few stitches and now stillness. In the
4 beginning, there was some mild coughing while eating.
5 Now just the constant hum of the suction machine and
6 the squeaky motor of the feeding pump.

7 In the end, all abilities once mastered were
8 lost and never regained. No matter how much we
9 fought, doing everything we could, Noah and Laine are
10 losing a tragically unwinnable battle against Batten
11 disease.

12 I'm going to close now but I'd like to
13 mention something. Decisions made by personnel at
14 this agency matter. You do have a tough job and we
15 realize that, but I believe my daughter, Laine, should
16 have had the chance to potentially participate in a
17 clinical trial testing enzyme replacement therapy for
18 Batten disease. People in this agency decided to
19 delay approval of the trial for some reason. The same
20 data package was taken to multiple sites in Europe and
21 children in Europe are now on therapy in the trial.
22 Because of this delay here in the U.S., Laine has

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

69

1 progressed and would no longer be eligible if and when
2 this trial starts here at home. We need to do better
3 for these kids here in the United States. Thank you.

4 (Applause.)

5 DR. EGGERS: Thank you very much, Tracy.

6 And I'm going to -- in the interest of time, we want
7 to get to the facilitated discussion. We're a little
8 bit over. We can make up time for that. We will have
9 some follow-up questions for you as we go -- as we
10 talk about the specific symptoms that are mentioned.

11 But I would like to give a round of applause to all of
12 the parents --

13 (Applause.)

14 DR. EGGERS: -- who we hope have spoken on
15 behalf of the rest of you in the audience. With that,
16 I would like to say how many people sitting out here
17 saw something, recognized something of your own
18 experience or perspective or that of your loved one by
19 hearing the range of the comments provided today?

20 (Hands raised.)

21 DR. EGGERS: Anyone that said I didn't hear
22 anything that resonated?

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

70

1 (No hands raised.)

2 DR. EGGERS: Okay. We didn't think so but
3 again, thank you. We're going to focus as much as we
4 can on particular effects and how they manifest
5 themselves. And we're not going to get to all of
6 them, but there are a few that we wanted to focus on
7 in particular because as Dr. Buracchio mentioned, they
8 are the hardest ones to grasp. And that is going to
9 be the cognitive and behavioral and some of those
10 other related symptoms. But we will focus on a number
11 of other ones.

12 Before we do that, we have a polling
13 question that will help put in context what all of you
14 in the room think are the most important effects that
15 affect you if you have the disease or your loved one.
16 This type is tiny. We wanted to squeeze as much as we
17 could into a polling question. But we want to know if
18 you can use your clickers, and if you're on the web,
19 go through the webcast, which of the following
20 symptoms currently have a significant impact on your
21 or your loved ones life as the patient. Please choose
22 all that apply.

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

71

1 So those motor deficits that we heard Tracy
2 talk about and some of the others, such as weakness,
3 spasticity, walking problems; the balance or
4 coordination problems, B; seizures, C; the sensory
5 impairment such as the vision loss that we heard about
6 or hearing loss; impaired cognition or developmental
7 delay; behavioral problems that we heard about
8 earlier, the hyperactivity, the aggressive behavior,
9 the hypersensitivity; bowel or bladder problems; pain
10 such as headaches, nerve pain or abdominal pain; or
11 something else if not mentioned. We heard many other
12 things even mentioned by the panelists that aren't on
13 this list.

14 (Whereupon, in response to polling, the
15 results are as follows: A. Motion, 3+%;
16 Balance, 33%; C. Seizure 20%;
17 D. Sensory, 30%; E. Impaired, 59%;
18 F. Behavioral, 52%; G. Bowel, 37%;
19 H. Pain, 44% and I. Other, 44%.)

20 DR. EGGERS: I think that's the number. So
21 how do we being. So we'll try to work through as much
22 as we can through these symptoms but it's -- you have

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

72

1 reiterated that you have this whole range of symptoms
2 that are significant with the most prevalent in the
3 group here being the impaired cognition or
4 developmental delay. Can I ask on the web what the
5 results are?

6 DR. VAIDYA: On the web, we have about a
7 majority of folks who have said motor deficits along
8 with impaired cognition or developmental delay,
9 behavioral problems and bowel and bladder problems.

10 DR. EGGERS: Okay.

11 DR. VAIDYA: And there was a good -- over
12 50% have said others as well.

13 DR. EGGERS: Okay. We'll delve into this
14 "other" category. And my -- the FDA panelists, if you
15 can jot down if any of these are surprising to you and
16 you want to follow-up on them in a little bit, please
17 do so.

18 So let's start with the cognitive effects
19 again and revisit some of things -- we heard Whitnie
20 talk about them. We heard Christine talk about them.
21 And actually, I think all the panelists talked about
22 them -- manifesting themselves from severe cognitive

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

73

1 effects to more mild ones, and if it's hard to lump
2 the cognitive and the behavioral, that's okay. Would
3 anyone in the audience like to share your experience
4 if you had cognitive up here that might differ from
5 what you heard before? We have some microphones
6 running around and there is the standing one but we
7 can bring a mic to you. Anyone want to share? Anyone
8 want to share even if it sounds like what was on the
9 panel and you want to reiterate?

10 AUSTIN NOLL: Yes.

11 DR. EGGERS: Okay. We'll bring the mic to
12 you. If you could just state your name and what the
13 underlying disorder is.

14 AUSTIN NOLL: Sure. Sanfilippo MPS III A.
15 I think it's the non-verbal, just not being able to
16 communicate is tough because you don't know how to
17 help them on a daily basis, so.

18 DR. EGGERS: The non-verbal. So you notice
19 we didn't have non-verbal and as I was reading
20 through, I thought well, where we would have put that.
21 How many of you had non-verbal symptoms in as "other"
22 that you -- okay, so if you could -- if non-verbal is

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

74

1 significant to you, could you raise your hands just so
2 we can get a sense?

3 (Hands raised.)

4 DR. EGGERS: Yeah. Let's focus on this one
5 a little bit more. Does anyone else want to follow-up
6 on the non-verbal effects?

7 ROY ZEIGHAMI: My son, Reed, is six. He has
8 Sanfilippo syndrome and he was asymptomatic until
9 about three years old, and we put him into a natural
10 history study, and about halfway through that, he --
11 we watched him lose all his speech, so going from
12 nearly a normal child to not being able to speak in
13 about six months. And it was a really painful process
14 because I watched him cry every day because there was
15 something inside of him that he wanted to get out and
16 he -- it just couldn't happen and so a very helpless
17 feeling as a parent to want to help your boy or your
18 girl and see them lose everything. And what I -- at
19 least my -- you know, what I felt was a lot of his
20 behavioral issues were due to frustration around
21 losing skills, and so maybe they were connected in a
22 way because he knew he used to be able to do something

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

75

1 and that he couldn't anymore and that was really hard
2 for him.

3 DR. EGGERS: Okay. Thank you. We heard
4 about the progression of the language challenges as
5 progressing slowly. Can I just ask does anyone have
6 an experience where it happened more rapidly? In the
7 back there.

8 JANA MONACO: Hi. I'm Jana Monaco and I
9 have two children with isovaleric acidemia and my son,
10 Stephen, is 16 and he was a late diagnosis at 3-1/2 so
11 he was the perfectly healthy normal child who just
12 didn't wake up one day. And he suffered severe
13 disabilities. It was a severe brain injury and so
14 everything that happened with him was abrupt, over a
15 24-hour period of time.

16 And he's affected in all of those categories
17 except for behavior. He's pretty calm and happy. But
18 I think the non-verbal is an issue because, again, he
19 was very verbal. And when a child like that loses
20 that ability, among other things -- he has a vision
21 impairment as well with limited vision -- over time
22 you work very hard to try to recover what you can.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

76

1 It's been 13 years since his crisis and I've
2 always described him as a child who his receptive
3 language and abilities is far better than his
4 expressive. But society doesn't quite always have
5 that patience or tolerance and we are always two steps
6 ahead of everyone. And so we have learned to
7 understand a lot of his abilities and his attempts to
8 try to communicate vocally over time but most often
9 it's dismissed. And when you try to look for
10 therapies and augmentive devices that try to fit that
11 particular child, because he doesn't have the ability
12 to use his hands, many things are not available for
13 him. And then you basically get shoulder shrugged
14 from the therapies, the therapists or the educational
15 people who just say they don't have anything else to
16 offer.

17 So we've had to be creative in our own ways
18 and try to explore therapies that are not approved by
19 FDA or the medical profession to try to tap into those
20 abilities which are costly. But we've also pulled him
21 out of the school system because we didn't feel that
22 they were supporting him in the way that he needed

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

77

1 that was most effective for him. So that is
2 frustrating because, you know, I think families know
3 things that professionals don't understand but they're
4 quick to try to dismiss it.

5 DR. EGGERS: I see a lot of heads nodding in
6 the room and resonating with that. Can I ask the FDA
7 panel, do you have any specific follow-up questions on
8 the non-verbal or the language challenges?

9 (No response/no questions posed.)

10 DR. EGGERS: Okay. What about the other
11 cognitive effects we heard about, impaired -- I'll say
12 impaired executive function, the decision-making, does
13 anyone want to follow-up on that and how you get a
14 sense of that? So we have one right up here and then
15 we'll go in the back.

16 MARY O'DONOVAN: Hi, I'm Mary, and I'm
17 actually going to speak in regards to my sister who
18 also has PKU. I have PKU as well. She was late
19 diagnosed -- because she was born before newborn
20 screening -- at 18 months of age. And she did receive
21 treatment on and off but then she went off diet for a
22 long period of time and had really elevated phe

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

78

1 levels. And when we got her back on diet -- well,
2 during that time period, for an example, I would take
3 her shopping and we had to get bananas. They were on
4 her grocery list. And I kid you not, five minutes --
5 I timed it -- it was five minutes to pick which
6 bananas she wanted to take home. And I event
7 importantly said, "Well, why don't you just -- I'll
8 just pick them." She's like, "No, I want to pick my
9 bananas. Just give me a minute." But it was five
10 minutes for her to pick bananas.

11 And then several years later after we got
12 her levels under control and got her doing better
13 again, we went shopping for shoes. And I said to my
14 mom as I went out the door -- I'm like, I might be
15 gone for a couple hours. You know, I'll see you in a
16 couple hours. But actually, I was back in 15 minutes.

17 We went to Payless Shoes and there's a lot
18 of choices there, so I was a little worried about that
19 first of all because I'm like, she can't -- you know,
20 how are we going to decide. She picked her shoes
21 within 10 minutes. And I said, "Okay, let's look at
22 all the other shoes." And she's like, "Nope, I like

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

79

1 these." She tried them on. She's like, "Nope, these
2 are the ones." And I'm like, "Are you sure?" You
3 know, look at these other options." "Oh, I've looked.
4 I'm sure. These are the ones I want." And she can
5 make decisions now and she's so excited and so happy
6 and so am I because I don't mind taking her shopping
7 anymore.

8 But it seems like a little thing, but it is
9 an amazing thing. It's an amazing thing to see that
10 ability come to someone. You don't think about that
11 taking brain snaps power to, you know, make a decision
12 about bananas or shoes but it does. And she can tell
13 the difference and that's what's exciting is how happy
14 she is about her abilities to do those things.

15 DR. EGGERS: Thank you very much. Any other
16 sort of cognitive -- or let's go onto the behavioral
17 effects that you experience. Regarding the behavioral
18 effects, let me ask a follow-up question so we can
19 tease this out. How many of you agree with -- I
20 forget who just said it about the behavioral effects,
21 when you see them, you believe they may be associated
22 with the frustrations with other challenges that your

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

80

1 child or you face. Okay.

2 (Hands raised.)

3 DR. KOHN: Okay. Does anyone want to
4 talk -- so I think we can understand that. What about
5 other behavioral effects that are not so much out of
6 frustration but are somehow different? Okay. In the
7 back there?

8 EDUARDO BALCELLS: Yes. My name is Eduardo
9 Balcells and I have a daughter, 10. Her name is Eva.
10 She has Leigh's disease which is a mitochondrial
11 disorder and the mitochondria are responsible for
12 providing energy to our body. And so Eva has
13 significant development delay in addition to -- her
14 behavioral issues are, that I wanted to comment on,
15 extend from the fact that because of her limited
16 ability to understand the situation, the environment,
17 she has moments of anxiety. So anxiety is something
18 that we deal with with Eva. She has -- we have
19 learned to have routines with Eva, habits and that --
20 this has allowed us to give her a sense of safety and
21 a sense of trust in her environment and in us.

22 The -- in addition, she has significant

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

81

1 motor -- loss of motor function, loss of motor tone so
2 her -- she's non-ambulatory. And so for us, the
3 neuromuscular manifestation of her disease is
4 something that we deal with quite a bit on a day-to-
5 day basis. And she's come a long way but again, a lot
6 of that's been from supportive care, therapies, in
7 addition, like I mentioned, the habits that she's
8 formed to allow her to sort of live in an environment
9 and understand what's next and sort of not get in a
10 situation where -- a dangerous situation where
11 safety's an issue.

12 But I think for her, the lack of being able
13 to understand and the lack of her being able to also
14 communicate gives her a sense of anxiety and that can
15 be very difficult. So I think the
16 psychiatric/neuropsych component is something that
17 falls into the "others" in her situation.

18 DR. EGGERS: So you're all reiterating the
19 interconnectedness, I'll say, of all of these
20 symptoms.

21 Actually, Whitney, I have a follow-up
22 question for you because we're hearing about anxiety

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

82

1 but you spoke about having no fear, and I was just
2 wondering if your son, if Reid ever does experience
3 fear or anxiety in contrast to the times that he feels
4 nothing?

5 WHITNIE STRAUSS: Right. No. He definitely
6 has periods of anxiety, you know, especially, you
7 know, if he were here today in a room full of a lot of
8 people, his pants would be down and he would be
9 running for the exit. I think -- and that's one of
10 the reasons why we're unable to kind of take him to
11 these social gatherings, you know, whether it be the
12 grocery store or restaurant, loud noises and, you
13 know, a lot of commotion, things going on around him
14 sort of cause him to be very uncomfortable. And that
15 progresses into some of the behavioral issues that we
16 deal with.

17 DR. EGGERS: So can I get a show of hands to
18 get these two contrasts? How many of you have your
19 child or you where the behavior is -- falls on that
20 aggressive -- I'm going to use inappropriate but I
21 don't mean it any bad way, just as a sense of the word
22 -- the behavior that falls on the spectrum that

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

83

1 Whitney's talking about when you thought of behavioral
2 problems, behavioral challenges?

3 (Hands raised.)

4 AUDIENCE MEMBER: (Off mic.)

5 DR. EGGERS: Oh, yeah, more like the types
6 of behaviors that Whitney's talking about, more that
7 would be seen to be inappropriate in public. Okay, so
8 a couple. Oh, maybe five or six.

9 Okay. How many when you thought of the
10 behavioral problems thought more of aggression, or
11 maybe they're all related? They're all related.

12 (Hands raised.)

13 DR. EGGERS: What about the anxiety, not so
14 much you listed that as a behavioral problem but
15 that's how it manifests itself?

16 (Hands raised.)

17 DR. EGGERS: Okay. All right. Any -- yes,
18 Dr. Buracchio.

19 DR. BURACCHIO: I was interested in Steve's
20 comment about the psychosis symptoms of delusions and
21 hallucinations. And I wanted to know if there was
22 anyone else in the audience who had experience with

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

84

1 those sorts of symptoms?

2 DR. EGGERS: We have a couple here. Would
3 you like to comment on it?

4 LIDNA MUUL: My grandson, Greg, has MLD and
5 he hears voices. And his first symptom that led to
6 diagnosis was a psychotic breakdown in school where he
7 heard voices telling him to hurt himself and other
8 people.

9 DR. EGGERS: Does that address your
10 question? Okay.

11 STEVE HOLLAND: There's -- between Tay-Sachs
12 and MPS, they do have the same storage heparan sulfa
13 and dermatan sulfa, so that's one reason I think it's
14 coming from the GAGs.

15 DR. EGGERS: How about --

16 HOLLON STEVENS: Hi. My name is Hollon and
17 my son has PKU. And I just wanted to make a comment
18 on some of the behavioral impacts that I've seen as
19 well and to reiterate some of Christine's comments on
20 the difficulty of maintaining the diet. And, you
21 know, I'm thankful for some of the aspects of PKU in
22 that it is diagnosed at birth and we do have a

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

85

1 treatment for it and my son will grow up, attend
2 college, and go to school, and, you know, I am
3 thankful every day for that.

4 However, it is not cured and we do look for
5 treatments, you know, enzyme replacement and, you
6 know, pharmaceuticals, liver cell transplantations.
7 We're looking for these innovative treatments and
8 hopeful that there is a bright future for those. And
9 in terms of what's available today, you know, it's a
10 daily formula intake that we rely on as 80 percent of
11 his diet in association with fruits, vegetables,
12 medical foods and, you know, a very severely
13 restricted, low protein diet. It involves weighting
14 the foods as Christine mentioned, very meticulous
15 recording of the intake, and then as levels get
16 escalated, even when they're slightly out of range,
17 you do see some of these behavioral impacts.

18 Some of those are, you know, aggression,
19 distractibility. I've seen Drake get very frustrated
20 easily.

21 One thing that's not up there is sleep
22 disruption and I've seen some studies recently showing

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

86

1 the impacts of sleep on learning, and so I wonder, you
2 know, what could be explored there. He sleep walks
3 sometimes when his levels are elevated and has bad
4 dreams and night tremors and that kind of thing. And
5 also, he's had some difficulties in school with
6 behavior when his levels have been elevated, so I just
7 wanted to share that with people.

8 DR. EGGERS: Thank you very much. Yes.
9 We'll follow-up more on the treatments and the
10 management of all of these things in Topic 2 and we'll
11 draw upon that as well. Peter has a question.

12 DR. COMO: Hi. Peter Como from FDA. Many
13 of you folks in the audience seem to suggest a variant
14 of a behavioral problems that is best described as
15 obsessive or compulsive behavior, either ruminative
16 thoughts or compulsive rituals. Is that something
17 that you're seeing a lot in your children? And if
18 anyone could elaborate on what those signs or
19 symptoms, that would be helpful.

20 DR. EGGERS: So can we get a show of hands
21 first for how many experience that?

22 (Hands raised.)

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

87

1 DR. EGGERS: Okay. So we'll go with you and
2 then we'll go with you right there.

3 DEAN SUHR: Hi. Dean Suhr. My daughter,
4 Lindy, who you'll meet in a little bit -- she's 33 now
5 -- has juvenile MLD. She actually was diagnosed
6 because of those compulsive behaviors. It was the
7 cognitive -- the loss of the -- slow loss of cognitive
8 skills that everybody tolerated and deferred and said,
9 Well, that's just behavioral and this and that and so
10 on, and lack of impulse control and so on. But when
11 she finally, if I could say that as almost with a sigh
12 of relief, when she had those picas and those really
13 impulsive behaviors, we, as a society, recognized as
14 oh, something's wrong. So, yeah, it is something that
15 we have to deal with but at least it's something we
16 can grab onto, too.

17 DR. EGGERS: Thank you very much, Dean. And
18 then right here -- I'll bring the mic around.

19 JILL WOOD: Hi. I'm Jill. I'm the founder
20 of Jonah's Just Begun-Foundation to Cure Sanfilippo
21 Incorporated. And I wanted to give you something a
22 little more light-hearted on the behavioral since this

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

88

1 is pretty heavy-duty stuff.

2 Sanfilippo syndrome is an MPS. It's MPS III
3 and it covers almost all of these things. But my
4 son's compulsion is licking. He likes to lick people
5 and it can be funny sometimes but absolutely
6 exasperating. We had a flight a few weeks ago and I
7 put him in the middle so he's trapped in the middle
8 and he can't run down the hallway and play with the
9 window and that sort of thing. And this gentleman
10 sitting next to me, I had the hell -- it was so awful
11 getting my son onto the airplane. I thought we were
12 going to get kicked off. I was like, "I'm never
13 flying alone with him." But Jonah jumped into this
14 guy's lap and started licking his face, licking his
15 hands and the guy just took it. I was just so
16 exasperated. I was like, "I love you, I love you."

17 DR. EGGERS: Thank you so much. Are there
18 other -- we could go on a range of other -- oh, go
19 ahead, yeah.

20 ROY ZEIGHAMI: Pica, is that how you say it
21 I guess? My son has Sanfilippo and he's constantly
22 chewing things and it makes him sick all the time

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

89

1 because he just puts everything in his mouth. And one
2 of the things that I think is confusing to a lot of
3 people about Sanfilippo syndrome is they see what they
4 perceive is aggression is just impulsivity on his
5 part. It's not actually aggression. So if he has a
6 cup and you stand in front of him, you're likely to
7 get the cup chucked in your face, right, and it's not
8 because he's trying to hurt you. It's just because
9 that's what he does with a cup that's in his hand.
10 It's just going to get launched. And he loves his
11 iPad. He loves to watch it. He'll look up at me.
12 He's happy to see me and he throws it right in my
13 face.

14 And so, you know, one -- I guess this isn't
15 something -- some of the things I worry about though,
16 these are -- how do you measure these kinds of things
17 for a treatment. And I guess that's what you guys
18 think about as experts, but these are really small
19 populations and treatment effects may be very small.
20 But I would be interested in, you know, these things
21 that are subtle and maybe even objective. How do you
22 measure these, right?

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

90

1 DR. EGGERS: I think that's why we're here
2 today is to hear these things that we don't usually
3 hear about in more technical settings. One here and
4 then we'll go to --

5 AUSTIN NOLL: And I just want to go -- you
6 mentioned sleep and sleep is critical. Our son,
7 again, who has Sanfilippo will go for weeks without
8 sleeping. And you just can't function. So you take a
9 look at, you know, aggression and everything else,
10 when you're in that situation, not to mention the
11 whole rest of the family who is awake, it's something
12 that really needs to be looked at, so.

13 DR. EGGERS: Can I get a show of hands who
14 put sleep in their "other" category?

15 (Hands raised.)

16 DR. EGGERS: Okay. So the Sanfilippo, okay.
17 Christine?

18 CHRISTINE BROWN: I just wanted to add that,
19 you know, some people have asked, you know, how the
20 FDA would measure these things. And I have to say as
21 a parent, I don't even know how to measure them. You
22 know, when my child decides to break out in song in

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

91

1 math class or, you know, I have to tell him eight
2 times to brush his teeth in the morning, or something
3 is happening, you know, I always wonder is that just
4 because he's having a bad day. Is it because he has
5 PKU? Is it because he's a boy? Is it because he's
6 six years old and this is what happens? And it's very
7 difficult as a parent to try to figure out how to
8 discipline when you're not quite sure of the causes of
9 them. And that's a constant struggle, I think, for my
10 husband and I is to figure out, you know, what is the
11 underlying cause of this. There's a lot of gray.

12 DR. EGGERS: Thank you so much.

13 WHITNIE STRAUSS: Well -- and I think
14 sometimes, if I can just add, there may be multiple
15 causes for an action. You know, let's say Reid, you
16 know, like your son, may have a cup he's drinking from
17 and he's going to chunk it at you. Sometimes it's
18 because it's empty, may need some more drink, and then
19 there's other times where he does it because that's
20 just what he does. When he's done with a cup, he
21 doesn't know how to put it down so he's just going to
22 drop it. So, yeah, how do you kind of determine is it

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

92

1 a behavioral thing? Is it a habitual thing? It is a
2 communication issues? There could be all of the above
3 for one action, so.

4 DR. EGGERS: I think this interconnected
5 nature, if you're going to follow-up on the docket, if
6 you have thoughts about how you tell -- how you
7 attribute an action that you see or behavior or an
8 effect, how you tie them together or what else you
9 think about when you're trying to figure out why is my
10 child behaving in this way, if I can make sense of it.

11 I have not gone to the web yet so I do want
12 to see if there are any comments that have come in so
13 far on any of the effects that we've talked about.
14 We'll still address others.

15 DR. VAIDYA: Son on the web, we have several
16 participants and they've mentioned non-verbal as a
17 symptom and also mentioned it actually severely
18 affects ability to learn and socialize and it also
19 makes it difficult to know if the patient is going
20 through pain or any other symptoms.

21 On the behavioral side of things, behavioral
22 symptoms and issues do affect the patients and due to

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

93

1 impaired cognition, so they don't understand the
2 danger of running into the road or also become very
3 anxious before going to a doctor's.

4 One participant also mentioned struggles
5 with executive functions, behavioral problems causing
6 inappropriate socialization.

7 And then few mentioned sleep issues as well
8 on the web.

9 DR. EGGERS: Okay. So they're reiterating
10 what they're hearing today. Ron.

11 DR. FARKAS: So sometimes when we're
12 thinking about measuring behavior, it's not actually
13 so clear if there is an unwanted behavior that goes
14 away, are there desirable abilities that go away. And
15 we've heard a little bit about that with some of the
16 medications I think. But I guess just when people
17 have been talking about how they think their child
18 might be doing, if they could just share more about
19 the different ways that they might separate out a good
20 day from a bad day, from problems and then good parts
21 of the day.

22 DR. EGGERS: So I think we have one comment

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

94

1 on there and then I think we'll ask the rest of the
2 folks to really expand upon that in your docket
3 comments. But we do have one comment back there.

4 CRISTY BALCELLS: Yes. My name is Cristy
5 Balcells and I have a little girl, Eva, who has
6 mitochondrial disease. I'm also the Executive
7 Director of a national organization, MitoAction.

8 And in representing my daughter as well as
9 other patients, including adults, who have
10 mitochondrial disease who have behavioral problems and
11 impaired cognition or developmental delay, I think
12 that there is a stigma in those symptoms, such as
13 depression, that it's situational. And I think that
14 adult patients in particular often complain to us that
15 their depression or their issues with executive
16 functioning are blown off as being situational because
17 they have pain or they have other physical issues
18 which greatly impair their quality of life and so
19 that's not really taken seriously as a symptom
20 category. And I think that it's a real struggle then
21 to definitively define those behavioral problems and
22 issues that are psychological, such as depression, as

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

95

1 true symptoms.

2 Similarly, I hear from parents quite often
3 who say that their children, who have features that
4 are on the autism spectrum but their children has a
5 mitochondrial disorder, that the treatment or the
6 focus in terms of approaching those behaviors is based
7 on as if the behavior was somehow caused by the child
8 or the family. But in reality, it's caused by the
9 inborn error of metabolism. It's caused by the defect
10 in the pathway, right, and if we could approach that,
11 maybe we could improve the behavior.

12 But I think that -- I appreciate the
13 opportunity for a regulatory agency like the FDA to
14 consider that sometimes those slippery slope symptoms
15 really could have the greatest impact for the patient
16 or the family.

17 DR. EGGERS: Thank you. I want to make sure
18 that we hear about if there are any symptoms that have
19 not been discussed today that you weren't able -- that
20 were in the "other" category that are really important
21 to your child or you if you are the patient and is
22 having an impact -- an affect on your day-to-day

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

96

1 living. Anything that's not been mentioned? Roy?

2 ROY ZEIGHAMI: One thing I've noticed about
3 my son is that it's hard to figure out whether he's
4 upset because he's in pain. And just the other day, I
5 noticed that sometimes within the span of 30 minutes,
6 he'll go through a cycle of crying and you're trying
7 to figure out if there's something wrong. And
8 sometimes -- and then he'll just, two minutes later,
9 he'll be happy. And so that seems to me it's not pain
10 or something like that. It's -- you know, he can't
11 describe it to me but there's just a range of emotions
12 that doesn't even seem to make sense to somebody --
13 you know, to us, right and that would see related to
14 the disease.

15 DR. EGGERS: Uh-huh. I see some heads
16 nodding in agreement about the range of emotions as an
17 effect. Are there any -- yes, Theresa?

18 DR. MULLIN: So, Sara, I think -- are you
19 going to get around -- or back to Ron's question which
20 is what does a good day look like, I mean more about,
21 you know, kind of the flip side of things not going
22 well but if there are things you see or you'd

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

97

1 associate with a good day for your child or for you if
2 you have the disease? That would be helpful, too.

3 DR. EGGERS: Sure. And before we go there,
4 I'm just going to tee up on the phone. If you are on
5 the web, we will have time for a call or two and we're
6 hearing -- we're primarily interested, I think, in
7 hearing about a symptom that has not been or an effect
8 that's not been raised today. Let me get a show of
9 hands to follow-up on Theresa and Ron's question about
10 how many have distinct good days versus bad days?

11 (Hands raised.)

12 DR. EGGERS: Okay. So can tell us --
13 someone want to tell us the difference between a good
14 and bad day? Yes, go ahead.

15 RHONDA CONNOLLY: Hi. I'm Rhonda Connolly
16 and i have two sons with PKU also and although we
17 don't have bad days, bad days as in some of these
18 disorders, the one thing though is that we have a
19 treatment and because there are not such physical
20 attributes, that my kids don't have some of the side
21 effects. When they take their diet, they feel great.
22 They concentrate well. They aren't anxious. They

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

98

1 aren't moody.

2 And so -- but the problems is as they get
3 older, as my son who is now 21, you feel good all the
4 time and you think well, I don't need to take that
5 today or I'm too busy. I'm going to be at my friend's
6 house. I'm not going to take that. Well, guess what?
7 The next day he is anxious. He is moody. He can't do
8 as well on his math and he does have issues. So part
9 of it is that you may not have those symptoms but
10 continue to take your diet and pills.

11 DR. EGGERS: Thank you. Is there any
12 example that's not -- that's outside of a treatment --
13 response to treatment, that's just natural
14 variability? Yes, did you have your hand up? Oh, did
15 someone -- okay, first we'll go to you and then we'll
16 go to Whitnie.

17 GORDON WINGATE: Hi. I'm Gordon Wingate.
18 My daughter, Jennifer, was born with MPS III-A and she
19 passed away with MPS III-A about five years ago. I
20 think -- you know, in my experience, a good day was
21 any time I had communication. I got laughter out of
22 her. She was happy. She just spontaneously burst out

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

99

1 laughing and I knew something I'd done had, you know,
2 put things right. And, you know, I think so much of
3 the frustration, the behavioral issues come from the
4 loss of language. In my experience, my observation,
5 the language gave structure to the world that went
6 away. When there's no language, there's no rules,
7 there no reason for us behaving one way or another. I
8 think back to the story of, you know, Helen Keller
9 before she discovered language. And that's the kind
10 of things, her inappropriate behavior, there's no
11 rules. I'm just going to walk over and go out here.
12 I'm going to walk out in the street.

13 But definitely, the good days were just when
14 I had communication, eye contact, sit and stare at me
15 for long periods of time and just interact personally.
16 And that was powerful.

17 DR. EGGERS: And could you, on a -- could it
18 vary? One day she has the communication ability and
19 the next day she doesn't and then some days later she
20 does so there was that variability in a week for
21 example?

22 GORDON WINGATE: Yeah. And a lot of it had

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

100

1 to do with just spending the time to draw it out of
2 her. I mean we had it in her I.E.P. that, you know,
3 communication was going to be how long could she
4 maintain eye contact because eye contact was
5 communication and it was very directly. I could see
6 that. So, yeah, there were good days. You know, they
7 were spontaneous when things were just going right
8 and, you know, she was just -- she just glows.

9 DR. EGGERS: Thank you very much. Would you
10 like to quickly follow-up, Whitnie?

11 WHITNIE STRAUSS: Yea. I mean I think we're
12 in a simil.ar situation where being non-verbal
13 definitely creates issues there for Reid. However,
14 you know, if I had to say, you know, a good day, I can
15 deal with the lack of speech with Reid. If he's
16 having a good day, he's patient. He'll take my hand
17 and put it on the door knob. He'll give me his cup.
18 I can live without speech.

19 It's the mornings that he wakes up and we
20 like to call him Tas, the Tasmanian devil because in a
21 three-minute timeframe, he's woke up, he's pulled his
22 diaper and clothes off, he's spilled a drink off the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

101

1 counter, he's pulled a bag of cereal down and it's all
2 over the floor, and he's dancing on my dining table
3 all within a three-minute period, and there are two
4 other children in the house who also need care. So
5 those days are the bad days where you just can't keep
6 up. He's always three steps ahead of you and you're
7 just trying your best to sort of manage the best you
8 can. I would take Reid non-verbal. I would take him
9 as he is if he would just be a little bit more
10 cooperative and a little bit more even keeled. That
11 would make a huge impact on our day and that would be
12 a good day for me. Given everything else he's dealing
13 with, I think that would make the biggest difference.

14 DR. EGGERS: Tracy.

15 TRACY VanHOUTAN: Just a quick little
16 different perspective from two kids in a terminal
17 disease, probably in the latter third of that disease.
18 So a good day for us is no seizures and I see that was
19 one of the lower reported outcomes here, but I don't
20 want folks to underestimate that because I think
21 either the medications we give our kids or the damage
22 caused by those seizures often can lead to some of the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

102

1 other symptoms that were mentioned.

2 But in addition to no seizures, getting a
3 smile from our kids is a good day. Our kids being
4 able to regulate their body temperature on their own
5 is a good day. Having bowel and bladder movements is
6 a good day for them. And not having sores when they
7 come home from school or an outing because they
8 myoclonis has caused them to bang into their
9 wheelchairs, that's a good day, too, so just a few
10 things from perspective of a child later on in a
11 disease.

12 DR. EGGERS: And can I ask, Tracy, are all
13 those things that you mentioned still achievable? Do
14 you still notice those with your children? Is it --
15 are those rare events or are they more common even if
16 they're variable?

17 TRACY VanHOUTAN: As far as seizures, I
18 think Noah's passed them. He's older. I think he's
19 passed the point where he's having a lot of seizures
20 now. They're so much brain atrophy so the no seizures
21 is more important for Laine. We get -- still get more
22 smiles from Laine. We don't see that with Noah

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

103

1 anymore. The body temperature regulation is more of a
2 problem with Noah than it is with Laine. Bowel and
3 bladder is both of them and they both continue to --
4 Noah more so has more myoclonis than Laine, but she's
5 travelling down that path as well. And secretion,
6 saliva management is also something that they're
7 dealing with now.

8 DR. EGGERS: Thanks. So we have one more
9 comment here and then we do need to go to the phone
10 and give folks a chance. We're a bit over our break
11 time but I think you will appreciate being as -- we
12 might shorten our break just a little bit and get
13 started on Topic 2.

14 GINA WILLIAMS: Thank you. Gina Williams,
15 vanishing white matter disease with an underlying
16 mitochondrial disorder from -- is my daughter. I just
17 wanted -- a little different perspective with
18 weakness. We haven't talked a lot about that but a
19 good day would be that she would be able to
20 participate with me, help me transfer her. She's in a
21 wheelchair predominantly. She can eat without food
22 getting stuck. That's what we call it, right, the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

104

1 swallowing issues.

2 The bad day would be that either it's the
3 heat totally wipes her out. She has no energy whether
4 it be that she sat up too long and she needs to rest,
5 she's leaning in her wheelchair. We have to set up,
6 hold your head up. She cannot participate in a
7 transfer. She can't even help with the lift. I have
8 a standing frame. She's not strong enough to
9 participate in that and just requires extra rest.
10 Food gets stuck is what we call it and the saliva
11 secretions and lots of underlying -- so just a little
12 bit of the muscle weakness and how that effects.

13 DR. EGGERS: Can I ask how old she is?
14 She's how old?

15 GINA WILLIAMS: She's 31.

16 DR. EGGERS: Thirty-one?

17 GINA WILLIAMS: Yes.

18 DR. EGGERS: Okay. Can we go to the phone
19 and see if -- operator, are there any callers on the
20 phone?

21 OPERATOR: Sure. If you'd like to ask a
22 question, you may press star one. Please make sure

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

105

1 you record your first and last name and make sure your
2 line is (inaudible) before doing so. Once again, you
3 may press star one if you'd like to ask a question or
4 make a comment. Give us one moment, please.

5 DR. EGGERS: Okay. While we wait, any other
6 questions from FDA?

7 (No response.)

8 DR. EGGERS: Any thoughts that are important
9 about the manifestations that haven't been mentioned?
10 Okay. in the back there?

11 EDUARDO BALCELLS: Again, representing Eva
12 with mitochondrial disease. Just tying into the last
13 comment with regard to motor strength and weakness.
14 Eva had strokes when she was in utero. She had
15 cerebellar strokes. She has significant ataxia.
16 She's not ambulatory but she can crawl. She has
17 intent to be able to grasp things and she uses an iPad
18 and which has been a blessing. I tell you, I thank
19 Steve Jobs every morning because it's amazing what
20 Eva's able to do.

21 But in her world, using the iPad, if she has
22 a bad day where she's weak and fatigued because of the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

106

1 motor issues, it impacts her neurologic issues and she
2 has much more dysmetria. And so she's' much less able
3 to grasp her spoon, feed herself, gets food all over
4 herself, is unable to enjoy the iPad which she really
5 enjoys and engages with. So again, the motor issue
6 ties in with the neurologic issues that she has.

7 Eva's blessed in the sense that she has not
8 had progressive metabolic strokes over time, but other
9 children with Leigh's disease do. So I think these
10 episodic events such as strokes manifest themselves in
11 different ways. But in Eva, it's manifested in
12 significant ataxia. And again, tying in that motor
13 issue with the neurologic issue is important for Eva.
14 So when she has energy and she feels strong, her
15 tone's better, she's able to do more and overcome her
16 neurologic deficits.

17 DR. EGGERS: Okay. Thank you. We have Ross
18 on the phone. Ross, you may speak. Operator?

19 OPERATOR: Mr. Bennett's line is now open.

20 ROSS BENNETT: Yeah. I would just say that
21 a good day for Collin is simply one where he -- we can
22 get him to sleep at night and where we were able to

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

107

1 keep him safe.

2 DR. VAIDYA: Okay.

3 DR. EGGERS: Thank you, Ross.

4 DR. VAIDYA: Thank you. Next caller,
5 please, Operator.

6 OPERATOR: We do have a question from Eileen
7 Linzer. Her line is now open.

8 EILEEN LINZER: Hi. I'm Eileen Linzer. My
9 daughter, Quinn, passed away last August of Nemann-
10 Pick Type A. We're a bit on the outskirts of a lot of
11 new issues. Our Quinn was not yet 15 months old when
12 she passed away, so its neurologic degenerative
13 Nemann-Pick. She -- her liver actually gave out
14 before she had a lot of those issues (inaudible). One
15 of the -- I had selected the "other" -- I'm sorry
16 (inaudible). It just kind of came up on the phone.

17 Her main issue as far as quality of life was
18 concerned while she was here was her feeding issue.
19 She was born and the day she was born, she started
20 what we thought (inaudible) was extreme spitting up
21 but, you know, it became apparent within just a month
22 or so that it was actually more of a neurological

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

108

1 issue. Her swallowing issue, we used to have to hold
2 her upright for a full hour after ever single solitary
3 feed. I have two other boys who kind of ran circles
4 around us while we did that. We couldn't move;
5 otherwise, she was much more likely to vomit and she
6 was very tiny to begin with so she couldn't afford to
7 lose it. That was -- she did get a G-tube and it did
8 help it but it never fully went away. So it was an
9 issue that I know had been raised on that initial
10 slide. It was on there, the swallowing. And perhaps
11 because of her age, that was why it was such a big
12 issue for us, but it was a very severe issue and it
13 really, tremendously impacted hers and our family's
14 quality of life.

15 DR. EGGERS: Thank you very much. You got a
16 lot of -- you can't see them, but you have a lot of --
17 a few heads nodding in the audience resonating with
18 what you're saying. Thank you. Do we have any more
19 callers? Okay. So that's it for callers. How about
20 a web summary of any comments on the web?

21 DR. VAIDYA: We have some folks on the web
22 who mentioned -- one participant mentioned that in the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

109

1 case of congenital disorders of glycosylation, there
2 are several obsessive behaviors where patients have
3 difficulty accepting any type of change. One
4 participant mentioned that the attenuated form of
5 mucopolysaccharidosis III show signs of short-term memory
6 loss. And in mitochondrial disease, someone else
7 mentioned that the autonomic dysfunction can be a
8 major issue. And for someone with MPS Type II, the
9 participant doesn't have congenital cognitive issues
10 but suffers from severe migraine headaches which last
11 five to six days every month and the pain is
12 crippling.

13 DR. EGGERS: Thank you.

14 DR. VAIDYA: Thank you.

15 DR. EGGERS: There's so much we haven't --
16 one more -- we'll take one more question -- or a
17 comment I mean. Sorry.

18 AMY MILLER: Hi. I'm Amy Miller and I'm
19 here with my son, Danny, and my husband, Ray. Danny
20 has Hunter syndrome and I was hoping to comment on the
21 last question up there. What's unique in our
22 situation is he, as a young child, had the symptoms

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

110

1 that many of you talked about, the extreme
2 hyperactivity. He was the Tasmanian devil. We had
3 our lamps screwed to the tables. We have nothing out
4 in the house. We had locks on things.

5 And being a progressive degenerative
6 disease, now we're dealing with like, is it Tracie,
7 your children. He -- at this point, he's 17, almost
8 18 years old and it's unique in the fact that we dealt
9 with those behavioral issues early on, but now we're
10 dealing with extreme medical issues that a lot of
11 people don't think it could possibly be the same disease
12 as it was when he was a young child. Physicians who
13 care for him now that never cared for him as a young
14 child can't believe that he could once run around,
15 ride a bike, feed himself because at this point, he
16 has not purposeful movements. He has seizures. He
17 has autonomic instability and storming. He has a
18 feeding tube because he was unable to swallow safely,
19 and he is complete care 24/7.

20 So our complete care from a young child was
21 keeping him safe and adapting our house to keep him
22 safe. We had a room that was all of his own that had

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

111

1 toys attached to the wall so he would play with them
2 instead of throw them to now complete care as far as
3 monitoring him for seizures, respiratory distress,
4 suctioning. So I just wanted to let you know that the
5 neurological symptoms change dramatically in some of
6 these diseases over time.

7 DR. EGGERS: Thank you very much. We are
8 going to have -- oh, go ahead, Larry, yes.

9 MR. BAUER: Yeah. At the recent narcolepsy
10 meeting, one of the unusual things was that a lot of
11 the people that came to the meeting had never met
12 other patients with narcolepsy which was kind of, I
13 thought, an interesting thing. And I was wondering --
14 in this group, we have a very diverse group of
15 diseases, and I was wondering how many of you are in
16 touch with other families with the disease and do you
17 find that the symptoms are similar or that there is a
18 great deal of variability between what your children
19 and families are experiencing?

20 DR. EGGERS: Let's see, so how about right
21 here and then if someone hasn't -- in the back hasn't
22 gone.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

112

1 GINA WILLIAMS: Hi. Gina Williams again,
2 vanishing white matter. Before, I was mitochondrial
3 and I was in touch with those and now that I have a
4 new diagnosis, we do -- it's not a support group
5 because there aren't that many of us -- but it's an
6 online and we are in touch and we share, and there are
7 five genes that are in effect for vanishing white
8 matter and the symptoms are very varied. My daughter
9 is very fortunate. I'm one of the least affected.

10 DR. EGGERS: Thank you. In the back.

11 JANA MONACO: Hi. I am also the Advocacy
12 Liaison for the Organic Acidemia Association and that
13 combines multiple disorders that are organic
14 acidemias. And many of us have the similar symptoms.
15 Some of the disorders are a little more involved,
16 involving their treatments and symptoms. Other --
17 especially if they were not screened at birth like my
18 son. So there are many of us that are in the age
19 bracket that he's in and older who have a lot of
20 severe disabilities and all of the different issues
21 related due to lack of screening.

22 However, many of the ones coming through

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

113

1 with newborn screening -- my daughter was screened
2 early because of my son -- do not exhibit all of these
3 kinds of issues. But then we work very hard to
4 protect them and there is a fine balance. But it's --
5 there are many variables that affect these children
6 and the adults that live with these disorders. So,
7 yeah, we actually are very connected through the
8 website, through the listserve and actually Facebook
9 pages as well, and we have a family conference coming
10 up this summer here in DC.

11 DR. EGGERS: If I could make a suggestion
12 for the advocates in the group, we've heard a lot
13 mainly personal stories and experiences, and I think
14 there's an opportunity for the advocates to expand
15 upon what Larry's asking about that variability from
16 what we heard today and across the patient population
17 that you work with.

18 We have -- okay, one more right back here.

19 UNIDENTIFIED MALE: My son has late
20 infantile Batten's disease and we are in constant
21 communication with the other families. It's a very
22 big part of learning about the disease and how to

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

114

1 manage day-to-day care for our children. And it's
2 remarkable that the story of the progression of the
3 disease is very similar in terms of diagnosis and, you
4 know, just the overall progression of the disease. So
5 it's very similar and it's very important for us to be
6 in contact with the other families.

7 DR. EGGERS: I'm going to have to put a time
8 out and have us go to a break. There were so many
9 issues we did not cover today. We didn't -- we heard
10 a lot but we didn't get into depth in some of the
11 issues, the motor and the other symptoms. Please feel
12 free on the web and in here to expand upon those.

13 So we're going to take a break now. I'm
14 going to suggest we come back -- try to be back at
15 11:15. We won't get started without -- you know,
16 without having most of you in the room, but if we can
17 shorten it to 10 minutes, then we can get back started
18 at 11:15. Thank you.

19 (Whereupon, off the record at 11:04 a.m.,
20 and back on the record at 11:21 a.m.)

21 DR. EGGERS: As people work their way in --
22 is this mice on? Can you hear me in the back? I just

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

115

1 want to thank you again for the Topic 1 discussion on
2 those effects that matter most, the neurologically-
3 related effects that matter most and encourage to
4 encourage you to contribute to the docket on those
5 effects and also remind you if you want to talk about
6 other effects that we haven't talked about -- Dr.
7 Buracchio put up a slide recognizing that there are
8 many effects beyond the neurological -- please feel
9 free to comment through the docket on those if we
10 didn't get to that, especially if you want to talk
11 about how the effects that you talked about today
12 stand in relationship to the other effects that you
13 have to deal with on a day-to-day basis.

14 We're now going to move into our second
15 topic which is really focused on treating and the
16 treatment approaches. We have heard quite a bit, you
17 know, as the panel comments from Topic 1, they worked
18 in treatment some into their panel comments and we got
19 some of it. So we want to build upon that now and
20 focus more on treatment approaches recognizing, of
21 course, that there are probably more variability in
22 the treatment approaches as there were in the symptoms

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

116

1 that were discussed today, so we're going to try to
2 work our way through this as much as -- to get as much
3 common ground as we can. We're not focusing so much
4 on particular treatments as much as to say what is it
5 that you think is important about treatment.

6 We have five panelists to kick off our
7 discussion, very similar to the morning, representing
8 a range of underlying IEM disorders and a range of
9 treatment experiences and perspectives. We're going
10 to ask each of them to go through with three to four
11 minutes of remarks, and we will start with Melissa,
12 please. If you can push your -- the button on your
13 microphone and hold it as close as possible so we can
14 hear you well.

15 MELISSA HOGAN: Hello, my name is Melissa
16 Hogan and I am the parent to a 7-year-old child named
17 Case with Hunter syndrome or MPS II as well his 8- and
18 10-year-old brothers. I am the founder of Saving Case
19 and Friends which is a Hunter syndrome research
20 foundation and the Hunter Syndrome Research Coalition
21 which coordinates families and foundations to find a
22 cure for Hunter syndrome. As a context for my

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

117

1 perspectives on treatment, a little background on
2 Hunter syndrome is warranted.

3 It involves progressive physical, cognitive,
4 and behavioral decline with an average life span of
5 approximately 12 to 15 years old untreated. At two
6 years old, when Case was diagnosed, he seemed like a
7 normal little boy with a little developmental delay
8 and some attention issues. He laughed and sang.
9 after diagnosis, he went on an FDA-approved enzyme
10 replacement therapy which involved a weekly 4-hour
11 infusion first in a hospital, then with a home nursing
12 and eventually, I was trained to do his infusion at
13 home which has allowed much more freedom and
14 flexibility in our lives and less medical trauma for
15 Case given that is a weekly 4-hour process for the
16 rest of his life.

17 ERT showed positive effects that we saw
18 because his liver and spleen reduced. He stopped
19 falling as much while he was walking, had more energy,
20 had more joint range of motion, was happier because I
21 believe he was in less pain. Breathing was easier so
22 he also began speaking more as well. It would be

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

118

1 great if it wasn't four hours or an IV infusion but
2 I'll take that if I it means it works.

3 Although he learned with difficulty for
4 about a year after diagnosis, he then rapidly began
5 losing skills. He lost 18 IQ points in 8 months.
6 Behaviorally, he became uncontrollable at times. We
7 had a CNA in our house five days a week because of
8 aggression towards his brothers and no sense of
9 safety. We had gates gating off all the rooms of our
10 house. He was strapped in a pediatric wheelchair with
11 a six-point harness when we were in public because of
12 lack of any sense of safety. I describe the
13 behavioral profile of Hunter syndrome as some autism,
14 ADHD, OCD, sensory processing, no sense of safety and
15 aggression.

16 His speech began to lesson to three- to
17 four-word sentences from nine words and he began to
18 stutter uncontrollably. He could not understand a
19 great deal of what was said. He could not even follow
20 one-step directions. He would easily choke on foods.

21 But at 3-1/2-years-old, following the 18
22 point loss of cognitive points, he was able to enroll

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

119

1 in a clinical trial that puts the enzyme he is missing
2 into his spinal fluid, initially, via an intrathecal
3 PORT-A-CATH and after 18 months, via lumbar punctures.
4 He has now been receiving lumbar punctures every four
5 weeks for over two years with anesthesia to receive
6 the medicine because of the failure of the initial
7 port and delay in approval for use of the new PORT-A-
8 CATH.

9 With that being said, here's how we
10 evaluated the decision to enroll in the trial despite
11 the potential risk of spinal and brain complications.
12 First was the potential for the drug. Slowing the
13 disease would be a win. Halting the disease would be
14 a huge win. Improvement was not even contemplated.
15 Life is most important and we'd take any shot at it.
16 We evaluated this with our own reading of the research
17 studies and speaking to other families and the PI.

18 Second in the evaluation was the risk of
19 doing nothing. We knew the natural history. We had
20 met other patients. To do nothing, to us, equaled
21 death. We knew how long a drug development and
22 clinical trials process took, and we knew this was our

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

120

1 only shot. That's how it is for many families and I
2 think you would agree. The trial that the FDA is
3 evaluating at any given time is truly the only shot
4 many of our children have to live because these
5 diseases are degenerative.

6 Only third in our evaluation was the risk of
7 the drug or the administration method. We would have
8 signed up for close to any risk because we know
9 otherwise he would die a slow, difficult, and painful
10 death.

11 What is most important to us about a
12 treatment? It's potential for life, survival, a
13 chance. Then, impacting other challenges such as the
14 behavioral aspect, the ability for him to function in
15 public and be safe and be independent in some ways and
16 have language. Third after that are also the medical
17 trauma challenges and a less invasive administration
18 method is actually more important than the risk that
19 it causes.

20 How can we tell that a drug is working?
21 Observation is the best method. Is he safe? Can he
22 walk? Can he be independent? What ADLs does he have?

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

121

1 And some thoughts I'd like to leave you with. Slowing
2 or stability is a win. We don't need a normal child.
3 We just want a living child.

4 Next, medical trauma is significant in these
5 children who require constant interventions, tests,
6 treatments and procedures. That has to be considered
7 when you contemplate the measures for clinical trials
8 and the administration method. Will they cooperate?
9 Will the measure traumatize them unnecessarily?

10 Regarding measures, cognitive testing on
11 these children is incredibly difficult, often
12 inaccurate, traumatizing, requires often Herculean
13 efforts by parents with planning and rewards, and
14 probably most importantly, excludes a large portion of
15 the patient population because there is a short window
16 where they are above the age where they can follow
17 directions to test but they have not yet lost all of
18 their cognition. The original inclusion window for
19 our trial was 15 points. When Case first tested, he
20 was above the criteria. So to wait for a fall -- he
21 then fell 18 points and had they not widened the
22 criteria, he would have fallen completely through.

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

122

1 Treatments and trials should be designed to
2 be tested and used across a range of genotypes, Krim
3 (ph)status and ages. The current narrow bands of
4 eligibility and automatic exclusions for things like
5 shunts both make enrollment difficult and do not
6 reflect the reality of many of our communities. For
7 example, a large portion of our community have shunts
8 and they are excluded in our cognitive trials.

9 Finally, and maybe most importantly, there
10 should be an expectation of compassionate access
11 passed the initial safety trial. Again, we just want
12 our child to live and any given trial or drug may be
13 the only shot they have.

14 DR. EGGERS: Thank you very much, Melissa.
15 And we'll move to Dean.

16 DEAN SUHR: Good morning and thank you for
17 inviting us and having this discussion. Hopefully,
18 it's as beneficial to you as it is to all of us.

19 As you've heard, the IEMs are quite
20 distinct. We share a lot of things in common but
21 there are a lot of differences. The disease that I
22 represent is metachromatic leukodystrophy. On the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

123

1 right-hand side of the screen, there is my daughter,
2 Darcee, who passed away at age 10 after what they
3 called a successful bone marrow transplant. She
4 engrafted. She lived through the transplant but she
5 had some post transplant rejection complications.
6 That was in 1995. She was diagnosed because her our
7 older daughter, Lindy, shown on the left there -- and
8 that's a pretty old picture -- she is now 33 with the
9 juvenile of metachromatic leukodystrophy. She can no
10 longer climb those stairs. She's in a wheelchair. We
11 have to feed her. She wears diapers and so on and so
12 forth.

13 We're blessed in that one of our two
14 children is still alive but ironically, that's the one
15 that didn't have a therapy. And would we go back and
16 make the decision differently? I don't think so. We,
17 like most parents, go into these trials and these
18 potential therapies with our eyes wide open.

19 MLD is one of many rare diseases and much
20 like rare diseases, about 50 percent of the cases of
21 MLD are the late infantile form with an onset of 18 to
22 24 months and its fatal in those kids generally before

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

124

1 they reach the age of 8, 9, 10-years-old. So it's a
2 very rapidly progressing disease and we are anxious to
3 not only have our kids thrive, but to just be alive
4 and to be able to communicate back with us.

5 The disease advocacy organizations are the
6 people that know where these families are and we're
7 quite anxious to work with the FDA and with industry.
8 We formed the MLD Foundation and literally travel
9 around the world meeting families, supporting
10 families, but also in the background doing a lot of
11 research work.

12 Families care about quality of life. It's
13 not just longevity. It's quality of life. We heard
14 this in the first session. And the therapies that are
15 proposed or addressed need to have that component.
16 And respectfully, I'm a big supporter of the FDA, but
17 the FDA model of do no harm, we need to watch with the
18 clock that says time to death. And do no harm, as
19 Melissa pointed out, when the outcome is death, the
20 risk-reward benefit tables turn quite a bit. And so
21 we're anxious for safe experimental therapies. We
22 want to make sure they're safe. But if the worst

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

125

1 thing that happens in a therapy is nothing, that's
2 okay. That's a good risk for us to take because we
3 hope and pray for the upsides.

4 The ideal therapy would stop progression in
5 the short term. We're seeing a lot of enzyme
6 replacement therapies. We have an enzyme replacement
7 therapy in clinical trial in Europe, not here in the
8 United States. There are issues related to getting
9 that application here. Those are things we want to
10 talk about.

11 There is a gene therapy combined with a bone
12 marrow transplant that is in Italy right now and we're
13 seeing wonderful results, and I hope the Vivian family
14 has an opportunity to speak in a little bit about
15 that. Their two children are here.

16 And we know there's no perfect therapy, but
17 three and four years out, we are guardedly just blown
18 away by the results. And we want to bring that to the
19 U.S. and we know there are a lot of issues that need
20 to be addressed and discussed with that.

21 One of the things that you asked us to talk
22 about a bit was consent. With over 50 percent of the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

126

1 MLD population being, you know, 3 or 4 years old by
2 the time you go through the diagnostic odyssey and are
3 considering something, those kids obviously aren't old
4 enough to give consent. So that discussion gets
5 deferred to the juvenile and adult forms. And I think
6 we need to be very aware with these neurological
7 diseases that when your cognitive abilities are
8 impaired, you aren't necessarily the best person to
9 give consent. And so we have to allow for the
10 caregivers and the parents and those that can take a
11 different perspective to be involved in that consent
12 decision.

13 Our third clinical trial is also only in
14 Europe. It's another gene therapy and we're concerned
15 that we have no clinical trials in the U.S. And just
16 as Melissa mentioned with compassionate use, we have
17 had numerous conversations with the folks that are
18 making these applications, and the FDA supports
19 compassionate use. Your rules allow that. And
20 industry says, Well, that's a good idea but the
21 reality is, at least with our disease, and I can't
22 speak for others, that they aren't huge advocates of

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

127

1 compassionate use. And the reason is not because they
2 don't care about the kids, they don't care about these
3 diseases, it's because the risk is too high of an
4 adverse event in a less controlled environment and
5 that will mess up their clinical trial. And they have
6 stakeholders and shareholders and all the normal
7 corporate stuff that makes that very challenging. So
8 it's a place where it's very, very awkward to have a
9 three-way conversation between advocacy groups and
10 families, the developers of a therapy, typically
11 academia or industry, and the FDA.

12 And to be perfectly honest with you, as much
13 as I -- and I'm not here to pick on anybody, to be
14 honest -- but this meeting is of advocates and we've
15 got some industry in the audience. When you go back
16 later today and tomorrow and next week, you'll have
17 closed door meetings with industry and with the FDA
18 and we won't necessarily be at that table. And we
19 need to have this kind of open exchange consistently
20 amongst all three parties even if it's uncomfortable,
21 because that's where all of this insight and
22 perspective comes from.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

128

1 Patient-reported outcomes was discussed a
2 little bit earlier. The world is turning on its ear.
3 PCORI is driving a lot of this but we, as advocacy
4 groups, have been active in this for a long time.
5 More and more data is being gathered and made
6 available as patient-reported data. And it's not
7 statistically valid because a nurse or somebody culled
8 that data, but it is statistically valid because it's
9 being reported over time by large sample sizes. So
10 it's a different sort of validation. And I think one
11 of the messages that we want to convey back to the FDA
12 is that patient-reported outcomes not only are good
13 data but it's insightful. We'll find out how many
14 kids have, you know, green dots on their thumbs or
15 whatever that other thing is that's not being captured
16 because somebody in academia didn't study it 10 or 20
17 years ago.

18 And my final comment is with regard to --
19 actually, two comments. One is with regard to
20 advisory panels. We're very interested as advocacy
21 groups in being on advisory panels but in many cases,
22 we are conflicted out because we have an educational

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

129

1 grant relationship with a -- maybe with industry or
2 something and a stack of paperwork they sign and we
3 sign to say there's no arm twisting, there's no
4 leverage, there's no promotion. And yet we come -- we
5 can't meet the SGE requirements for conflict of
6 interest. And with an organization such as MLD and
7 other rare diseases, we are the experts. We've seen
8 hundreds of families and literally dozens of
9 researchers at their homes, at their sites, and we're
10 the experts and we can't participate.

11 And the final thing is what can we do for
12 you? I sat with an FDA representative a number of
13 years ago now, and they very casually just said back
14 to me, well, we have all these regulations and we
15 respect and we like those regulations but we are the
16 people that can make the change. We are willing to
17 have an act of Congress if that's what it needs to
18 help change the world which is changing with regard to
19 therapies. And we need to know where we can help you
20 with that. I think PDUFA V is indicative of those
21 sorts of things. So, thank you.

22 DR. EGGERS: Thank you so much, Dean. And

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

130

1 now we'll have Jennifer.

2 JENNIFER PAYNE: Hi. I just want to extend
3 a thanks to the FDA and the CDR for having the
4 opportunity to share my opportunity to share my
5 patient perspectives on the current approaches to
6 treating IEM. My specific connection is to PKU
7 diagnosis, 1973. The provision of clinical care is
8 through the University of Maryland and in the very
9 early years under protocol through Maryland's newborn
10 screening program that involved intensive home visits,
11 blood phe drawing, and dietary monitoring with
12 provision of medical food which is also the emphasis
13 of my comments, but I would like to acknowledge there
14 are some other treatments -- the open dialogue session
15 that follows.

16 Medical food is the treatment that I depend
17 upon to this day for health and survival, to perform
18 academically, socially, and professionally, one that
19 spared me a lifetime of institutional care and saved
20 my children's lives. This patient-focused dialogue
21 offers a channel of communication that I think can be
22 very beneficial to assure that the FDA is meeting its

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

131

1 commitment in implementing PDUFA-V which is why we are
2 here today, thanks to the Congressionally-mandated
3 responsibility known as FDASIA.

4 I have been asked to address attributes of
5 an ideal treatment. While the diet has its
6 shortcomings, there have been milestones. And I think
7 the FDA shares my concerns warranting a 21st Century
8 approach to nutritional management of PKU that
9 includes access to innovations. First and foremost,
10 the attributes: Prevention: In the words of former
11 Secretary Sebelius, preventing illnesses before they
12 become serious and more costly to treat helps
13 Americans of all ages stay healthier.

14 Key Congressional witness, Dr. Shuren of the
15 CDRH, at November's FDASIA's hearing highlighted
16 another key attribute, accelerated access, and
17 reinforced the need to speed innovative new products
18 to market without compromising safety.

19 And in the case of PKU, unnecessary delays
20 and affordable access to conventional treatments, game
21 changers within the category of medical food and
22 emerging pharmaceuticals leads to disease progression

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

132

1 and devastating outcomes that are 100 percent
2 preventable for limited, underrepresented, underserved
3 population as the PKU adults.

4 In the history of biochemical genetics,
5 there is no greater invention than treatment which
6 takes the form of a diet that can prevent severe,
7 devastating neurological toxicities and virtually
8 eliminate disease manifestations. In untreated
9 adults, there is increase in mental illness,
10 psychological disorders like depression and phobias,
11 anxiety, and neurological deterioration, seizures,
12 tremors and paresis; hence, the wheelchair.

13 On the bottom row or bottom quarter there,
14 there is a visual representation of the positive
15 outcomes not possible without early and continuous
16 treatment but the story does not end here. Children
17 born to pregnant with untreated PKU have severe birth
18 defects. Microcephally, congenital heart defects,
19 developmental delay, and mental retardation. There is
20 no cure. This would be idea.

21 Other attributes that I would look for in an
22 ideal treatment -- this is something that's

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

133

1 personalized given the variability of the genetic
2 mutations in the enzyme and consideration should be
3 given to individual patient variables and their
4 specific metabolic needs. This requires a multi-
5 disciplinary team approach and maybe combination
6 therapy that's afforded to all patients with PKU.
7 Regardless of the treatment or the inborn error, the
8 risk versus the benefits must be weighed, discussed
9 with the metabolic team to assure patients are meeting
10 their goals and the treatment plans optimize outcomes.

11 The FDA is a shepherd of resources and that
12 includes medical food. I do not want to see PKU
13 patients handicapped anymore by an inefficient system
14 for which medical food fits no paradigm. The
15 incentives under PDUFA V need to be extended to the
16 medical foods industry, the small business innovators
17 who hold my lifeline. Thank you.

18 DR. EGGERS: Thank you very much, Jennifer.
19 And now we'll move to Roy.

20 ROY ZEIGHAMI: So I'm Roy Zeighami. I've
21 told you a little bit about my son already. He's six
22 years old and has Sanfilippo syndrome. I won't dive

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

134

1 into what that is. I think we've talked about it
2 enough already. But I'll talk a little bit about what
3 we're giving him today to try and manage his symptoms
4 and what seems to work and what doesn't.

5 One of the things that showed up in animal
6 models was that you could give Sanfilippo mice
7 Genestein in very high doses and actually manage the
8 underlying cause of the disease. You could reduce the
9 substrate that was built up in the mice. And with
10 nothing to lose, we tried Genestein on our son in a
11 comparable dose as to what was given in the mice. And
12 what we saw in the period that we gave him between 3
13 and 4 was, I mean, just extremely rapid decline. It
14 seemed to have no effect. We took him off.

15 And so there was -- you know, there wasn't
16 any assurance that this substance was helping him and
17 that's obviously evidence that what might work in a
18 mice doesn't seem to necessarily work in humans. And
19 so we were left with treatment that basically managed
20 his symptoms. Some -- one of the symptoms is
21 aggression and we give him risperdal to manage his
22 aggression and we found that that made him easier to

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

135

1 manage in school, less aggressive and less impulsive
2 and amitriptyline at night to help him sleep. And both
3 of those things have been, you know, very good for him
4 in terms of managing those particular symptoms.

5 Now the downside of giving him those drugs
6 is that it makes lethargic the next day. And so, you
7 know, as a parent, I have to sleep, right. We have to
8 live our lives and so I sort of feel some guilt about
9 giving him something that causes him to wake up a
10 little sluggish in the morning but it's a choice that
11 we make because it seems to help our family live our
12 life.

13 And what I would like to see in terms of
14 treatment is not just something that seems to treat
15 the symptoms but something that attacks the underlying
16 cause of the disease. I mean Sanfilippo is caused by
17 a well-known gene defect that causes a missing enzyme
18 that causes a well-known substrate to build up in the
19 brain, and yet there is nothing that we can try here
20 in the U.S. and no trials here in the U.S. to treat
21 that.

22 In terms of what I'd like to see, I think

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

136

1 something that managed his hyperactivity would be
2 excellent, something that helped him sleep without
3 waking up the next morning feeling drugged, and
4 something that managed his impulsive aggression. And
5 I think, you know, managing and stabilizing his
6 cognition, I mean we can him risperdal, but that's not
7 keeping him from slipping away from me, right. And
8 let's see, I think a homerun for me would be is if I
9 could take my son to the grocery store and walk
10 through the grocery store holding his hand and
11 shopping without him ripping everything off the
12 shelves. I mean that would be awesome, right. I'm
13 not expecting the kid to get a medical degree someday.
14 I just want him just to live a manageable life.

15 And finally, I just want to talk a little
16 bit about consent. I think there may be a perception
17 among the scientific and regulatory community that
18 patients need tons of data. And what I would say is
19 that, you know, the average run-of-the-mill parent is
20 not going to be able to look at some animal data
21 around longevity or whether they can swim through a
22 maze or something like that and make a decision about

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

137

1 treating their son. They're going to trust what the
2 doctors tell them, right. And so I would avoid just
3 releasing tons of data to patients. I think it needs
4 to be boiled down by the sponsor and by the -- you
5 know, the industry sponsor and then the doctor that's
6 running the trial. And that needs to be boiled down
7 to simple language that parents can understand.

8 One of my concerns is that we don't
9 necessarily want to create huge hurdles either for
10 opportunities to try treatments. One of the things
11 that we see in Sanfilippo, there is no newborn
12 screening for Sanfilippo and so every kid that goes
13 into the trial is symptomatic. By definition, they've
14 been found -- unless they're a younger sibling of a
15 parent that got -- or an older child that got
16 diagnosed, they, by definition, have symptoms and
17 that's why they were found and yet a treatment might
18 work differently in a symptomatic patient than in a
19 newborn. And yet I don't want to wait for animal data
20 that says, yes, this treatment works in newborns. I
21 mean the way every industry sponsor is going to test a
22 drug, they're going to get an animal model, they're

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

138

1 going to test it on the newborns, and there is some
2 sign of efficacy and proof of safety, that's enough
3 for me because the option of not doing anything is
4 certain -- it's a death sentence, right.

5 And, you know, we absolutely need trials in
6 the U.S. There's an intrathecal ERT trial similar to
7 what most have talked about and the company, the
8 sponsor couldn't get it opened up in the U.S. and we
9 tried everything from moving to Europe, asking for
10 compassionate access, and there's just, you know, no
11 opportunity, and that's a hopeless feeling as a
12 parent.

13 I think we want some reasonable idea of
14 safety but I don't think we necessarily need proof of
15 efficacy before we try something in a phase one/two
16 trial.

17 I know that this is a shocking thing,
18 probably, for most people to hear, but, you know, my
19 son may live 10 more years if we don't treat him, but
20 his quality of life is rapidly decreasing. And I
21 think if I tried something today with a reasonable
22 belief and doing my homework that it might help him

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

139

1 and he died, I would know that I'd died trying and
2 that would be something that I could live with. And I
3 want that chance to try for my son.

4 And I know that -- I respect you guys so
5 much for what you deal with because no one's ever
6 happy with the FDA. Probably people complain if you
7 let something go through that shouldn't and, you know,
8 we want you to move faster. And, you know, I think
9 our job as patient advocates is to make our
10 perspective clear on these catastrophic diseases. We
11 need to go to Congress. We need to give you guys air
12 cover to let you know that you can move as fast as
13 possible so that you guys don't have the fear of being
14 dragged up in front of Congress. And that's our job
15 and we're going to continue to do that.

16 And I think one of the brightest spots of
17 hope for us in the Sanfilippo community, above the
18 ERTs that are being developed, is gene therapy. And
19 in terms of what might be very interesting to see in a
20 consent form, you know, one of the therapies that's
21 being developed is being done right here nationwide,
22 and they're using an AAV9 vector. And yet they're

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

140

1 using that same vector for SMA, for other diseases,
2 and maybe there's safety data from those other trials,
3 and maybe that data can go into the consent form. And
4 I don't know whether that safety data translates but I
5 think that's very interesting information, and
6 maybe -- you know, maybe that could translate to some
7 degree, so, thank you.

8 DR. EGGERS: Any -- you finished --

9 ROY ZEIGHAMI: Yes.

10 DR. EGGERS: -- your -- oh, sorry. Thank
11 you very much, Roy.

12 ROY ZEIGHAMI: Sure.

13 DR. EGGERS: And finally, we will have
14 Andrea.

15 ANDREA SMITH: Hello. My name is Andrea
16 Smith and I have a 6-year-old daughter, Katie, who was
17 diagnosed with an inborn error of metabolism. She has
18 a MELAS-like syndrome and was recently also diagnosed
19 with Type B pyruvate carboxylase. Katie has low tone
20 and transient muscle weakness. She rarely sleeps, has
21 severe temperature dysregulation, gut dysmobility, and
22 has seizures. When we received Katie's diagnosis, we

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

141

1 worked with a pediatric psychiatrist named Dr. Stanley
2 Greenspan and moved to Bethesda. We're originally
3 from Texas. She's also being treated at Johns Hopkins
4 and Columbia University.

5 Katie has a sweet disposition and is well-
6 behaved but she does experience extreme anxiety as she
7 does not understand why her body receives several
8 different messages. Dr. Greenspan taught us how to
9 cell regulate he by carefully monitoring, on a daily
10 basis, and working with her doing something called
11 Floortime. It's basically a play therapy to keep her
12 emotionally regulated, to take her to higher levels of
13 thinking and understanding the world around her. It
14 is very successful as we continue to do Floortime.

15 Since the first year of her life, she has
16 received speech therapy, physical therapy, and
17 occupational therapy. We spend more than the average
18 family on food and antioxidants. Now that we have
19 learned that her IEM takes so much work for her to
20 convert nutrients into energy, we are constantly
21 trying new things that she eats, things that we've
22 noticed that work or don't work. We know that her

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

142

1 cells have an impact on her ATP and her mitochondria
2 regulatory function which is why we believe all this
3 expensive therapy has kept her alive.

4 Katie maintaining cellular metabolic
5 homeostasis is a 24/7 job for me and is the most
6 difficult because, well, you know, it affects
7 everything she does, how she feels, her seizures, her
8 brain disorganization, her blood pressure is all over
9 the place, and her central nervous system.

10 She's also been taking a mitochondrial
11 cocktail for over a year now and we have not seen any
12 improvement. And I asked my neurologist slash
13 geneticist okay, well, now what? What do we do? And
14 he said, you know what, that's the million dollar
15 question. I get this question from everybody and I --
16 and he says I don't know what to do. You just have to
17 treat each symptom as you, you know, walk this path.

18 So I Googled some of her symptoms and I
19 found a wonderful organization called MitoAction whose
20 mission is to support those affected with an IEM or a
21 mitochondrial disease. They don't necessarily give
22 medical advice but they offer practical advice for

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

143

1 patients to manage their symptoms and family support.
2 Also, MitoAction has helped our daughter improve her
3 quality of life because sometimes when I don't know
4 what to do, there are others there along the way to
5 hold my hand.

6 Since there is no cure, I would want to know
7 the modulation of her gene or mitochondria oxidative
8 phosphorylation to match the work of her ATP
9 hydrolysis. I don't know if that makes any sense to
10 you but as I understand and experience what my child
11 goes through daily is that the food she is eating is
12 not converting enough energy or oxygen to make proper
13 ATP. Thus, enter mitochondrial dysfunction. Then
14 this creates the whole messed up metabolic
15 homeostasis. Are there post transational
16 modifications and metabolic alterations that can be
17 adjusted? I don't know but I'm certainly looking into
18 it in Europe.

19 I certainly do not want to use children as
20 human guinea pigs. Do we continue to use experimental
21 mice in labs? The informed consent should clearly
22 communicate in laymen's terms how long the experiment

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

144

1 has existed, outcomes and statistics, and how many
2 participants. Also, has the medicine been tested to
3 rule out any damage to the mitochondria?

4 I believe a mandatory class should be taken
5 for a certain amount of hours for parents to complete.
6 Do not go over the paperwork the same day in the
7 clinic, for example. Parents need time to digest the
8 information. A second mandatory class to ensure the
9 understand exactly what they are committing to. There
10 should be a Q and A day especially put aside with the
11 specialist who created the trial.

12 After that, parents, I believe, must have a
13 waiting period before they sign their child up. For
14 example, let's just say like three days. I'm sure for
15 many parents and because of their desperation, they
16 would do anything to help their child and my fear is
17 they may make an emotional decision not realizing some
18 of the side effects and risks.

19 In conclusion, parents of children with IEMs
20 spend a large portion for their time trying to get
21 their medical needs met through insurance. There
22 should be more awareness and advocating for IEMs just

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

145

1 like children who have cancer or leukemia. That's
2 all.

3 DR. EGGERS: Thank you very much, Andrea.
4 And again, if we could give these parents and the
5 individual living with the PKU a round of applause.

6 (Applause.)

7 DR. EGGERS: We thank you very much for
8 setting up a great foundation to a discussion. We
9 won't be able to follow-up on every point that you
10 have made, but I think you really set the stage
11 explaining the range of perspectives and the range of
12 experiences that you've had. I'm going to ask again
13 just so we get a sense of how many people, as you were
14 listening out here, how many patients and caretakers
15 heard your own perspectives or experiences shred?

16 (Hands raised.)

17 DR. EGGERS: Anyone who has experiences or
18 perspectives that are widely different?

19 (Hands raised)

20 DR. EGGERS: Okay. So it sounds like there
21 is some common ground here and we'll delve further
22 into that.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

146

1 To start, we're going to have a polling
2 question just like we had in the first topic. This
3 just gives us a sense of what your experiences are.
4 And you're on the web, then you should have this
5 polling question as well.

6 What therapies have you used to manage your
7 or your loved ones condition, and please check all
8 that apply: dietary restrictions/supplementation
9 medical foods; enzyme replacement therapies; bone
10 marrow or organ transplantation, that's C; other
11 prescription medicines to help support the condition
12 such as anticonvulsants or psychiatric medications;
13 non-drug treatment such as dialysis, G-tubes or
14 splinting; use of assistive technologies, a broad
15 range of them from wheelchairs to readers, etcetera;
16 other therapies such as behavioral, physical, speech,
17 or occupational therapy; or something else or none of
18 the above, then you would mark H.

19 (Whereupon, in response to polling, the
20 results are as follows: A. Dietary, 68%;
21 B. Enzymes, 28%; C. Bone, 12%; D. Other
22 prescriptions; 64%; E. non-drug; 10%;

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

147

1 , use of assistive technologies, 60%;

2 G. Other therapies, 68%; and H. None, 8%.)

3 DR. EGGERS: Okay. Again, we have the wide
4 range of experiences represented here, a little less
5 experience collectively with enzyme replacement
6 therapies and with bone marrow transplantation for
7 several reasons. On the web.

8 DR. VAIDYA: We have a very similar
9 distribution on the web as well.

10 DR. EGGERS: Okay. Thank you. Okay. We're
11 going to touch upon some of these now in more depth
12 and feel free to help with some follow-up questions.
13 And we will first start with the enzyme requirement
14 therapies. We've heard the experiences shared and we
15 might have heard some from Topic 1.

16 What we're really looking for in this
17 discussion is to get at what specific neurological
18 effects are they addressing well and how do you know.
19 Would anyone like to comment more on that from their
20 experience? Yes, Steve. Hang on one second.

21 STEVE HOLLAND: Steve Holland, MPS I. So my
22 children started ERT in 1998 and at the current

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

148

1 dosing, there's no evidence in their condition that it
2 improves the neurologic effect of the disease. In
3 animal studies they have to give like 20-fold in order
4 to get any treatment from that. So absent doing it
5 intrathecally, providing the enzyme that way, it's
6 just not going to cross the blood-brain barrier under
7 the current technology.

8 DR. EGGERS: Okay. Thank you. Anyone else
9 want to share their experience?

10 DEAN SUHR: And I would say one of the other
11 things is -- it's up here Sara -- sorry --

12 DR. EGGERS: Oh.

13 DEAN SUHR: -- that CNS versus PNS and the
14 effectiveness of enzyme therapy in both aspects of the
15 nervous system is something that is not consistent and
16 something we need to learn more about.

17 DR. EGGERS: Okay. Any specific downsides
18 of these treatment that you would like to highlight?

19 AUDIENCE MEMBER: (Off mic.)

20 DR. EGGERS: Just the enzyme replacement
21 therapies at this moment?

22 AUDIENCE MEMBER: (Off mic.)

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

149

1 DR. EGGERS: Okay. We'll have Amber and
2 then we'll go back there.

3 AMBER MORGAN: Hi. Amber Morgan. My
4 daughter has MPS I. She only received enzyme therapy
5 for about 17 weeks during the time in which she was
6 receiving a bone marrow transplant. And the downside
7 for us definitely was the fact that they had to access
8 veins on a 13-month old child every single time you
9 went in. And even when she had the port, it was
10 easier but there are infusion issues that children can
11 take on too much fluid and then have issues with blood
12 pressure and other concerns. And after she had her
13 port taken out from transplant, we were back to
14 peripheral vein use and that was a big bummer for her.

15 Also, a downside would be sitting for 4 to 6
16 hours with a 2-year-old attached to a wire in a crib
17 that just wants to be running around. It gets tangled
18 up and they get wrapped around them so that's not
19 pleasant.

20 DR. EGGERS: Thank you, Amber. Back there?

21 NADIA BODKIN: I don't have a downside to
22 the enzyme. I have a downside to the other

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

150

1 treatments. I don't know if you --

2 DR. EGGERS: Okay. We'll probably get to
3 those other treatments and then if we don't, we'll
4 come back to you. What's your name?

5 NADIA BODKIN: My name's Nadia.

6 DR. EGGERS: Nadia, okay. Are there any --
7 go ahead, Jennifer.

8 JENNIFER PAYNE: I can't really comment on a
9 downside of the enzyme replacement therapy because for
10 PKU, we actually have one that's in Phase III clinical
11 trials right now. So that remains to be determined.
12 But a downside for me as far as the inclusion
13 criteria, I've had the consent forms in my hand but
14 one of the criterion is looking at the phenylalanine
15 level. And Christine mentioned in the earlier
16 session, there's a very narrow therapeutic window and
17 they're looking at adults that are above six. I don't
18 meet that criteria because I'm stable. So it is a
19 concern to me as we, you know, roll out these new
20 therapies. It's anticipated this may be something
21 likely I'll see. In the future, how you transition
22 adults with PKU who are in stable metabolic control to

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

151

1 an enzyme, it doesn't really seem that that's what
2 they're -- right now they're just focusing on the
3 levels. And we've seen that with Kuvane FDA approved
4 in 2007. It's used to help stimulate residual enzyme.
5 There's different PKU: hyper phe, classical, so you
6 might have different functioning forms of the enzyme.
7 This is used to boost the activity as an adjunct
8 therapy to a diet.

9 The response can be different responses and
10 I think (inaudible) can probably comment better on
11 that. But efficacy is looking at a 30 percent drop in
12 the phe levels and I think as far as the neuro
13 cognitive effects, that's probably something still in
14 study but maybe they could address. But it's an
15 ongoing process and --

16 DR. EGGERS: Thank you, Jennifer. Any
17 follow-up questions? Melissa, go ahead.

18 MELISSA HOGAN: I would just make two
19 comments about downsides of ERT, the first being -- we
20 had the workshop yesterday on immune tolerance and I
21 think that's a very important issue to continue
22 exploring both in intravenous ERT as well as

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

152

1 potentially in intrathecal ERT. Obviously, very
2 important to me.

3 And the second, as I mentioned, was the
4 medical trauma aspects of constant interventions on a
5 weekly basis, then in clinical trials and then with
6 additional tests that a lot of these kids are required
7 to undergo.

8 DR. EGGERS: Thank you. Anything --

9 STEVE HOLLAND: Just one other thing. I
10 mean not to state the obvious, but obviously the cost
11 and the time that's involved. We're willing to accept
12 those things so it's not a -- but you know, the second
13 generation small molecule, taking a pill obviously
14 would be much more preferred for all the kids on ERT.

15 DR. EGGERS: Thank you. We've had some
16 discussion -- I know there is some in the audience --
17 I know Amber, I think -- about bone marrow or organ
18 transplantation, and I just wanted to spend a few
19 minutes to follow-up on if anyone wanted to share
20 their experience. We will ask Amber to come up and
21 just spend a few minutes on what you saw as the
22 effects, especially the impact it had on the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

153

1 neurological effects from the bone marrow
2 transplantation.

3 AMBER MORGAN: When my daughter was
4 diagnosed, she was 11 months old and the reason that
5 we found her diagnosis was not neurological. Really,
6 at that point, she was only six months old when I
7 started questioning doctors as to what was going on
8 with her. By nine months, when I finally said she's
9 not babbling and that was a sign to me that there was
10 something going on, then they finally started looking
11 a little more serious at her.

12 And throughout transplant, she still had yet
13 to do things like walk on her own. Rolling over was
14 still not something that she was able to do. Sitting
15 up on her own was quite a struggle. She learned,
16 actually, while she was in transplant to do this
17 motion (indicating with head up and down) with her
18 head which was a lot of fun because then when she came
19 down, there was a crib side that she would smack. So
20 we had to start padding the crib for her while she
21 went through transplant. And she wasn't speaking
22 still yet. She learned to do the mamma, dada thing

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

154

1 what she was in transplant.

2 And so we worked a lot with all the other
3 therapies. The physical therapy and occupational
4 therapy and speech therapists came in every day when
5 we were there. And by the time she got out, she was
6 up to being able to sign six words. She still was not
7 walking on her own but she was cruising her room for
8 that period of time. I can't think of many other
9 things that she gained. I mean she really seemed like
10 she was supposed to go through transplant. She was
11 just much stronger when she got out.

12 Once we got home, it was about three months
13 that went by before she started walking on her own and
14 speaking words and she chose a good one. Block was
15 her first word. So, yeah, had good effects.

16 DR. EGGERS: Thank you very much, Amber. So
17 we've heard very different experiences with bone
18 marrow transplantation. Does anyone else want to
19 share their experience with that? Right here.

20 BECKY VIVIAN: Hi. My name is Becky and I
21 am here with my two children, Eli and Ella. Our story
22 is a little bit different. My kids -- Eli, 20 months

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

155

1 ago, was diagnosed with metachromatic leukodystrophy,
2 otherwise known as MLD. We were told basically, take
3 him home and enjoy the rest of his life, because
4 there was no real treatments for the disease. In
5 researching, we found out that there was indeed bone
6 marrow transplant. But after we researched more, we
7 found out that for MLD, just this disease specific,
8 the mortality rate was at least 40 percent. And in
9 the last 20 months, we met a lot of people on Facebook
10 and through the MLD Foundation, and anyone who has had
11 a bone marrow transplant, they are still progressing
12 with the disease and they are still dying.

13 We -- by the grace of God, we got into a
14 clinical trial in Milan, Italy and I lived there for
15 four months with Eli last year and he got gene
16 therapy. Ella and I --

17 DR. EGGERS: Eli's raising his hand.

18 BECKY VIVIAN: -- oh -- Ella and I just got
19 home about four weeks ago from her gene therapy. We
20 lived there for another four months. She was in the
21 hospital for 64 days. For Eli, we had to pay for
22 everything because he was accepted out of compassion.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

156

1 We were going to opt to not do a transplant because of
2 all the harmful side effects for this particular
3 disease.

4 As you can see, they are doing amazing.
5 They left Milan after four months of being there.
6 None of them -- neither one of them were on any drugs,
7 no immunosuppressives, obviously, because they're
8 using their own cells that are just manipulated. And
9 they're both doing wonderful and Eli was number 10 in
10 the world and Ella was number 11.

11 And all I can say is I really hope -- I'm
12 not here for them because they already went through
13 treatment. I'm here for the ones that come after them
14 and hopefully, other people get this opportunity,
15 because when you talk about treatment, when Eli was
16 diagnosed, unfortunately, the neurologist kept turning
17 us down, there's nothing wrong, there's nothing wrong.
18 So it also has to start there. I think that more
19 people need to be more aware of these types of
20 diseases because had he -- you know, had I waited and
21 not trusted my gut, we would have never even gotten in
22 that trial and then these two would be just living out

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

157

1 the rest of their life.

2 So I could just ask you, the FDA, just look
3 at these treatments as another option because there's
4 nothing here in the United States. And I had to leave
5 my other two kids for eight months to live in Italy
6 and it's obviously affected our whole family. And --
7 but hopefully, they can live, you know, a nice life
8 right now, so thank you.

9 DR. EGGERS: Thank you very much, Becky.
10 Any follow-up questions on what we've heard?

11 (No response.)

12 DR. EGGERS: Okay. Any comments from the
13 web on these topics?

14 DR. VAIDYA: We have some comments not
15 directly related to the -- to what we were hearing in
16 the room, but we do have some web participants who've
17 mentioned the issues around compassionate use of drugs
18 and a participant mentioned concerns about applying
19 standard clinical trial parameters to the IEM trials.
20 Also, some other treatments have been mentioned such
21 as IV pamidronate for mucopolidosis. And for Gaucher,
22 there are substrate reduction therapies but the side

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

158

1 effects make it very difficult for the patients.

2 DR. EGGERS: Okay. Thank you. We've heard
3 quite a bit about medical foods both from Jennifer's
4 comments and from some comments earlier with regard to
5 medical foods in PKU.

6 Are there any other experiences with medical
7 foods or other dietary supplementation that you would
8 like to share at this point? Okay. We'll go back
9 there first because the microphone is back there and
10 then we'll come up here.

11 JANA MONACO: Hi. The organic acidemias
12 also thrive on the medical foods and the formula
13 they -- we have a -- there is a formula devised for
14 each particular disorder that leaves out the offending
15 amino acid that they cannot metabolize. So for my
16 children, their isovaleric acidemia is an ability to
17 break down leucine. So both of my children, they
18 consume part of their diet with natural protein. My
19 daughter, because she does not have the same
20 neurological defects that my son has, gets her natural
21 protein from foods where my son gets it from a liquid
22 pre-mixed formula all ready. But they are both

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

159

1 supplemented with the leucine-free formula that is
2 vital to keeping them alive.

3 DR. EGGERS: Can I ask do you see effects?
4 Can you see changes in their neurological symptoms and
5 effects?

6 JANA MONACO: Oh, absolutely. My son not
7 having the restricted diet at birth along with the
8 amino acid supplements which is he -- they both are on
9 Glycine and levocarnitine, Carnitor. And that helps
10 them to rid their body of the isovaleric acid that
11 builds up. So since he didn't have it for the first
12 3-1/2 years before diagnosis, there were, I guess,
13 different times where he was almost at risk. And at
14 18 months, he was sick but unfortunately, when he was
15 hospitalized, it was not discovered. No one
16 identified the disorder so it went undetected.

17 But as soon as he was put on diet, he
18 remained stable metabolically for the past 13 years
19 and he's had a lot of hospitalizations, five surgeries
20 in the past three years. And though he's had a lot of
21 critical moments, he's remained metabolically stable
22 throughout everything. And my daughter remains on the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

160

1 restricted diet with the e-formula as well and the
2 amino acid supplements and she's protected. She is
3 11, finishing out fifth grade.

4 If we don't maintain that status of
5 maintaining that level with these foods, we can see
6 her get a little lethargic and just not, as we say,
7 you know -- they're off as we will say and they begin
8 to wilt, so a huge impact.

9 DR. EGGERS: Okay. Thank you so much.
10 Right up here.

11 CASEY CONNOLLY: My name is Casey Connolly.
12 I'm a lifelong PKU patient. Sorry to bug you again
13 about PKU. I know there's a lot of patients in here.

14 DR. EGGERS: We want to hear about PKU, of
15 course.

16 CASEY CONNOLLY: So basically, PKU, growing
17 up through your childhood, the hardest thing is, you
18 know, being normal and being cool around other people.
19 And growing up eating these fake processed foods that
20 your mom has to cook for you everywhere you go, and
21 you have to bring a fake lunch with fake cheese to
22 school and have kids wonder what are you doing; why

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

161

1 are you eating that, it makes life growing up rather
2 difficult.

3 And then as getting into high school,
4 luckily enough my mom has been fully engulfed in the
5 PKU community and I was able to get into clinical
6 trials and be able to be a testing dummy basically for
7 all -- for Kuvan, let's say. And I did start Kuvan
8 since I was 14 and even since then, that's changed my
9 life into a whole 180 because now I can eat like a
10 straight vegetarian. And by all means, it's been one
11 of the greatest things that I have been through in my
12 entire life and been able to be a part of.

13 But now it's going through seven years of my
14 life where I'm still on the same drug, I'm still doing
15 the same thing. Yeah, I have to take over 30 pills
16 (holds up a baggie of pills) a day in order to sustain
17 just a vegetarian diet that's consisting of carbs,
18 fruits and veggies. And in order to do that, I have
19 to take 30 pills. Every meal I go to, I have to bring
20 a bottle with me and to whip out the pills. So when
21 I'm out with friends, if I go on a date, I got to
22 bring my pills with me and I got to explain the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

162

1 situation every single time. It gets tedious and it
2 gets frustrating. And the problem with that is being
3 a PKU patient, the number one thing that you need to
4 do to stay healthy is take your medication. And when
5 I have to take 30 pills a day every single meal, when
6 I have to drink a formula twice a day every single day
7 which consists of 500 calories per drink which sums up
8 to 1000 calories a day, aka supplementing half my
9 meals a day, which don't get me wrong -- it tastes
10 disgusting, but I have to do it in order to move on.
11 But that takes away half my meals every single day of
12 where I want to eat, you know, a fruit salad or
13 something delicious tasting.

14 And so the fact that going through this,
15 having all these steps and processes, the volume of
16 medication that I need to take just to become a
17 vegetarian, which I'm not even cured yet, but it's
18 just -- it's just temporary is making my life so
19 tedious that I -- I'm watching my little brother go
20 thought he same thing because he does the same -- he's
21 14 with PKU, but it makes him not want to take his
22 medications. And because he resisted doing it and

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

163

1 which my mom has to force it upon him, he refuses even
2 more because he's in those teen stages where you don't
3 want to. And when he does that, then all the symptoms
4 come, lack of focus, temper. I mean I -- when I don't
5 take my medication in school and I have to take tests,
6 I sit there and I just twiddle my thumb. You can't
7 focus at all and so your temper is problems.

8 And now as graduating, when I'm going in the
9 job market now and in three years, I'm going to have
10 to start paying for this on my own -- which don't get
11 me started on how expensive this stuff is -- it's
12 going to be a whole new ballgame.

13 And so all I'm saying is just to make lives
14 -- like Kuvan stepped my life way above where it was
15 before. But now the next step is decrease the volume.
16 Like I can't sit here and take four more hours of each
17 day taking these medications, gulping down 30 pills a
18 day and sitting here drinking this big shake of bland
19 tasting stuff in order to survive. It sucks but I
20 mean I will do it until the day I die because I can't
21 go back to where it was. But just decreasing the
22 volume, that would be the next progressive step that

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

164

1 we could make in making lives better.

2 DR. EGGERS: Thank you very much, Collin.

3 Collin, right?

4 CASEY CONNOLLY: Casey.

5 DR. EGGERS: Casey? Sorry. Thank you,

6 Casey.

7 JENNIFER PAYNE: Can I add to Casey's

8 comments?

9 DR. EGGERS: Sure, Jennifer.

10 JENNIFER PAYNE: I think that he did a great
11 job showing the issues with compliance, not only the
12 diet but also the pill burden with Kuvan. As you can
13 see, it's life-changing for him. I'm not a consumer
14 of Kuvan. You have to be tested to respond to the
15 medication. But he makes a good point with the
16 medical foods. Essentially, it's medication. You
17 have to take it religiously, like I said earlier, to
18 perform on a day-to-day basis. And that -- you know,
19 just the slightest change and your phe levels, you can
20 feel the effects.

21 And I just want to say for me, you know, the
22 medical food is the treatment for me. For now, I'm a

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

165

1 pharmacist. I need the utmost, you know, attention,
2 focus and concentration, you know, to do my job. But
3 the point is I -- the -- he points out some of the
4 limitations with the diet, the high carb load. It's
5 not perfect but, you know what, the diet got me
6 through three pregnancies, three healthy children, and
7 if that is not enough -- you know, that's testimony to
8 the power of the phe-restricted diet right there.

9 DR. EGGERS: Thank you so much. If you're
10 looking at the agenda, don't be nervous. We get to
11 keep going. We have -- we only need about 15 minutes
12 for the public comment session so we're going to keep
13 going on this topic and stretch it out as much as we
14 can.

15 If you have signed up for the public comment
16 session, we're going to ask you to limit your remarks
17 to three minutes and we will be pretty tight on that
18 three minutes because we do want to make sure we have
19 since we're going to limit it to 15 minutes so that we
20 can have this conversation go as long as possible.

21 Are there any other treatments that you want
22 to focus on before we go into a discussion on clinical

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

166

1 trials? Yes, Julie.

2 DR. BEITZ: Hi. I wanted to follow-up on a
3 comment that Ms. Hogan made earlier and it's not
4 necessarily about a specific treatment but to -- if
5 I've quoted you correctly, you said there should be an
6 expectation of expanded access pass the initial safety
7 trial?

8 And if I could have you just explain a
9 little bit more about what you mean. Do you mean that
10 if someone's enrolled in a safety or efficacy trial
11 and they have completed the trial through the time
12 points for assessing safety and efficacy, that they
13 should then allow to stay in the trial and get the
14 treatment? Or do you mean that they can get off the
15 trial and do something different?

16 MELISSA HOGAN: Thanks for the question.
17 No. I think the extension trial, I mean, obviously, I
18 think is a no-brainer. But I think in these very
19 severe degenerative diseases where you have a very
20 short timeframe in which to try to save your child,
21 once a drug is shown to be even somewhat safe, I think
22 it is incumbent upon industry to expect that the

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

167

1 community, once they see that a drug is safe and has
2 some level of efficacy, that patients are going to
3 want to save their children.

4 When my son is seven and he's learning to
5 snorkel right now and climbing rock walls and playing
6 computer games and his best friend is dying at the
7 same age, that's a very difficult thing for a
8 community to sit and accept when we see a drug that's
9 shown safety and even at this point shown efficacy.

10 DR. EGGERS: I think we'll delve a little
11 further in this in a few minutes. Any other questions
12 on any specific treatments or treatment types?

13 (No response.)

14 DR. EGGERS: We haven't been able to talk
15 about the very important, more supportive care
16 treatments, the other prescription medications that
17 you've taken, the importance of, as we're hearing, the
18 physical, occupational, and speech therapies and
19 behavioral therapies. So we'll encourage you to share
20 those experiences through the docket if you have a
21 chance to submit additional comments.

22 Any other comments on treatments on the web?

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

168

1 DR. VAIDYA: We have a web participant who
2 mentioned his son or daughter has Sanfilippo and
3 they're -- he treats the child with supplements but
4 there is no evidence that these actually work. They
5 also are on a low sodium, anti inflammatory diet
6 regimen which has helped reduce the joint pain.
7 That's it.

8 DR. EGGERS: Thank you, Pujita. Okay. We
9 want to make sure we get to follow-up on the great
10 comments that we heard from the panel on the informed
11 consent in the clinical trial participation. So
12 before we do that, we have a few polling questions
13 just to understand the experiences and perspectives in
14 the room and on the web.

15 And the first one is have you or your loved
16 one ever participated in any type of clinical trial,
17 study, experimental treatments for IEM?

18 (Whereupon, in response to polling, the
19 results are as follows: A. Yes, 41%;
20 B. No, 55%; C. Not sure, 5%.)

21 DR. EGGERS: Okay. So we have about a dozen
22 of you in the room have not had any experience and

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

169

1 about 10 of you I believe had had experience. On the
2 web?

3 DR. VAIDYA: About two have had experience
4 on the web.

5 DR. EGGERS: Okay. Can I get a show of
6 hands from those of you that have said no?

7 (Hands raised.)

8 Of those of you that said no, how many of
9 you wanted to be in one and could not for some reason?

10 (Hands raised.)

11 DR. EGGERS: Okay. So there's another
12 polling question which -- and this is a very tough one
13 and believe me, no one's going to hold you to the
14 responses of this. This just gives us a general sense
15 of your thoughts toward clinical trials. Today, think
16 about your situation today, you or your child's
17 situation today. If you or your loved one had the
18 opportunity to participate in a clinical trial to
19 study an experimental treatment -- let's think of
20 something that's either a medical treatment or a
21 transplantation -- which of the following best
22 describes your thoughts: Yes. Of course, it would

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

170

1 depend on many factors but I am generally willing to
2 consider participating. No, I would probably not
3 consider participating. Or maybe, I'm not really sure
4 whether I would be generally willing to participate.

5 (Whereupon, in response to polling, the
6 results are as follows: A. Yes., 100%;
7 B. No, 0%; C. Maybe, 0%.)

8 DR. EGGERS: Okay. All right. You made me
9 read through all of these really tough response
10 choices here. You could have just stopped me and said
11 "that's a dumb question." On the web.

12 DR. VAIDYA: On the web, we actually have 85
13 percent who've said yes; 5 percent who said no, and
14 then 10 percent who are unsure, uncertain.

15 DR. EGGERS: If you're on the web, if you
16 could provide a comment if you were one of that said
17 generally no about why. Okay. So we now have a sense
18 of the perspective shared in the room.

19 And then to follow-up this discussion, I'm
20 going to throw one more think at you which is a
21 scenario just to help set the stage. And when we
22 answer the next questions, try to put yourself in this

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

171

1 position, that you or your child has the opportunity
2 to consider participating in a clinical trial for an
3 experimental enzyme replacement therapy or something
4 similar to that, that the clinical trial is a phase
5 one, first-in-human study involving approximately 10
6 patients, so it's never been studied in humans before,
7 and for this trial, there is less animal data
8 available to evaluate the safety than is typical for a
9 first-in-human study of this type. Therefore, the
10 benefits and the risks of this experimental would be
11 highly uncertain.

12 So are question is what thoughts first come
13 to your mind when you hear this scenario? What
14 questions would you have? So I'll open it up. I'll
15 come out here first and then we'll -- yeah, right
16 there.

17 STEVE HOLLAND: Yeah. I think the key to
18 that question is less than what is typical because our
19 understanding is that what is typical is killing lots
20 of large mammals when that is unnecessary. So I
21 think -- my thoughts on that are that yes, it needs
22 to be treated-tested in animals and I don't think any

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

172

1 of us are willing to do anything that's not, but it's
2 the extent for these rare diseases of putting them
3 through the same rigorous, you know, thresholds that
4 for something that's affecting a lot of diseases, a
5 lot of people when ours is affecting, you know, fewer.

6 DR. EGGERS: Thank you. Let's go to Roy and
7 then we'll go to Austin.

8 ROY ZEIGHAMI: I think it would depend on a
9 couple things. One, is there a reasonable treatment
10 already available for the disease, right.

11 DR. EGGERS: Okay.

12 ROY ZEIGHAMI: I would accept more risk if
13 there's nothing. And secondly, it would depend on
14 where my child was in the course of the disease. If
15 it was very early and young and there was hope that I
16 could wait and see some data, then maybe I would sit
17 on the sideline. But if the window is very short
18 relative to the time of the trial, I would put him in,
19 no doubt about it.

20 DR. EGGERS: Okay. Thank you. Julie, would
21 you like to follow-up and then we'll go to Austin.

22 DR. BIETZ: I just wanted to clarify that

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

173

1 maybe one of the ways that the amount of data is less
2 comparable to what we're used to having is not so much
3 the number of animals but the duration of the animals'
4 exposure. So for example, if you we would normally
5 have a treatment in animals for six months and in this
6 case we only had one month of treatment, how would
7 that impact your thinking about that. So we would not
8 have very much experience with treatment over anything
9 longer than say a month. How would people feel about
10 that?

11 DR. EGGERS: Okay. Austin, would you like
12 to go and then we'll go to Tracy.

13 AUSTIN NOLL: Thanks.

14 DR. EGGERS: I think there's a hand up over
15 here.

16 AUSTIN NOLL: Can you hear me?

17 DR. EGGERS: Uh-huh.

18 AUSTIN NOLL: To me -- so you've got two
19 questions to ask, right? You have safety and efficacy
20 and it's been said many times here that -- and I think
21 everybody or most people in this room agree that
22 safety is the primary thing you need to take a look

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

174

1 at. I think we're all willing to take more risk. We
2 have to. My son's going to live three more years. So
3 what are you going to do, you know? Sorry.

4 I'm not in a riskier -- I can't be in a
5 riskier situation. Just give him a chance. Give
6 these kids a chance.

7 DR. EGGERS: Thank you, Austin. There was a
8 hand -- we'll go to Tracy first and then we'll come up
9 here to you.

10 TRACY VanHOUTAN: I think I agree with the
11 previous comments. Just, you know, give our kids a
12 chance. To your question -- statement about the
13 animals, in the genotype of these animals, are we
14 seeing any improvement even in the shorter timeframe?

15 DR. EGGERS: Oh. This was a scenario so is
16 that a question you would want to know about?

17 TRACY VanHOUTAN: Well, a scenario was given
18 to us by the panelists. I was asking the question --
19 I need a little bit more information about that
20 scenario to answer.

21 DR. EGGERS: Okay.

22 DR. BEITZ: Right. There would be -- Donna,

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

175

1 maybe you could answer. What I was getting at was the
2 duration of treatment to assess safety but if -- but
3 maybe Donna, you can talk about the efficacy.

4 DR. GRIEBEL: I was just going to say if we
5 were going into phase one in children, we have to have
6 some sign, whether it's in a -- some scientific
7 rationale and proof that there is some hope of
8 efficacy in the children. So in this scenario, yes,
9 we would say that there is some evidence that there
10 might be efficacy that would support going into the
11 children. So the -- what Dr. Beitz was going after
12 was going after was the duration because the duration
13 and a treatment in these children with diseases that
14 are lifelong diseases, the treatment would be expected
15 to be as long as the child lived. And we learn in
16 these animal studies what happens over time in the
17 animals by -- they're sacrificed and we look at their
18 tissues to see what happened to find out what might
19 be -- we might be able to predict and what we should
20 be looking for in the children for a toxicity. So
21 that was the question about how you would -- how
22 different parents might factor that information in

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

176

1 into a consent form about knowing what the amount is
2 relative to what is usual in the long-term safety.

3 TRACY VanHOUTAN: Okay. Let me finish with
4 this comment. A lot of our kids are dying. We aren't
5 looking -- they're dying. They're drowning in the
6 middle of the ocean. We aren't looking for the Queen
7 Mary to come by and take us to the next coast. We
8 need a lifeboat. We may not expect to be on therapy
9 for life because in a lot of these conditions, we know
10 there are second generation treatments coming along.
11 Give us the lifeboat, please.

12 DR. EGGERS: We'll go here.

13 STEPHANIE BOZARTH: My name is Stephanie
14 Bozarth and my daughter has MPS IV. And actually,
15 it's an inborn errors of metabolism but it doesn't
16 typically affect the brain, so we are fortunate in
17 that sense. But her life expectancy is still pretty
18 short so there are other parts of the inborn errors of
19 metabolism that will affect her long-term longevity.

20 When it comes to this question, we do have
21 experience with enzyme replacement therapies and we do
22 know from what we've seen in the past, that when

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

177

1 you're introducing a known protein into the body,
2 there is a less probability of toxicity. I think
3 there does need to be safety data. But where can we
4 learn from what we've already been doing with enzyme
5 replacement therapies and make that a little more
6 concise so that we can get these therapies out quicker
7 and sooner to the children?

8 And like many other MPSs, time is not our
9 friend and my daughter did, fortunately, get to get in
10 a clinical trial at the age of five but her growth
11 plates would probably be dead by the age of eight,
12 which she turned eight a couple of weeks ago. So, you
13 know, it really meant a lot to be able to get on that
14 clinical trial as soon as possible.

15 So I would absolutely, knowing what the
16 risks were and that there was some safety and efficacy
17 and that we've been doing enzyme replacement therapies
18 for 10 years now -- we know about them, so.

19 DR. EGGERS: Thank you very much. I just
20 want to put a call out to the Operator, if you could
21 open the phone lines for anyone to give a final though
22 on the phone.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

178

1 I have a question I would like to follow-up
2 with which is to -- for those of you in the room, and
3 it's probably a smaller group of you, who have a child
4 who could because they're either old enough or they
5 have some capacity to, could take part in the decision
6 about whether to participate in a clinical trial, what
7 is most important from your perspective to communicate
8 to address how the trial and informed consent is
9 communicated to them? Maybe some different things
10 than you've seen in your past experience. Steve?

11 STEVE HOLLAND: We've been through clinical
12 trials with our kids both as minors and as adults, so
13 we have some -- so it's been done -- handled
14 differently in those situations. But even as a minor
15 and as a child, I think involving them in the process
16 at the level they're able to understand and getting
17 them to sign on the paper so that they buy into it at
18 the level they can is very important as far as down
19 the road as, you know, when you're going through some
20 of the constraints of the trial and the effort that it
21 takes to be in it just to get them -- they're okay in
22 it.

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

179

1 But even in our case, our kids are
2 somewhat -- are a little cognitively impaired. They
3 still look to us as their parents to provide them that
4 assurance and comfort, so I really thing their buy-in
5 is more just an add-on to the parents.

6 DR. EGGERS: Okay. I see a lot of heads
7 nodding. So we'll go with Christine and then did you
8 -- sir, did you have your hand up?

9 CHRISTINE BROWN: My 8-year-old was all
10 ready to sign up for a clinical trial for PKU using
11 the enzyme replacement therapy, and I mean the
12 clinical trial is for 18 and up. But we -- I had an
13 opportunity a couple of years ago to meet somebody who
14 was in the phase two trial. She laid out the shots
15 for him. She laid out the thickness of that needle.
16 And he said, you know what, Mom, I still want to do
17 it. So I think that with kids, it's maybe showing
18 them some of the things and what would be involved and
19 how big that needle might be or, you know, what the
20 procedure actually looks like, you know. And if he
21 had the opportunity and if he feels that strongly
22 about it, you know, maybe down the road, it's

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

180

1 something that he can participate in.

2 DR. EGGERS: Thank you, Christine. We're
3 going to have to move on in the interest of time but
4 there -- well, first of all, any pressing questions
5 from the FDA panel? Okay, yes, go ahead, Rachel.

6 DR. WITTEN: Hi. My name is Rachel Whitten.
7 I'm from Gene and Cell Therapy Deviation. And, you
8 know, our products are different. When we give this
9 product, you don't know how long it's present. It
10 may, you know, die in -- it's a live vector and we
11 don't know how long this -- the product is going to
12 work. Maybe it's one month, maybe two years or three
13 years.

14 What we started doing recently, when we
15 receive the protocol from the sponsor, we usually try
16 to involve patient representative. You're going to
17 start -- we ask the patient representative start with
18 us with pre R&D meeting. Look at the protocol. Read
19 the consent form and go through the protocol and let
20 us know would you enroll your child in this clinical.

21 But what happened -- again, we (inaudible) a
22 lot of rare diseases but sometimes we just cannot find

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

181

1 patient representative who will work with us and on
2 this point, we do need your help.

3 DR. EGGERS: Okay. So I will put a shout
4 out for our colleagues in the Office of Health and
5 Constituent Affairs who help organize the patient
6 representative program that Rachel is talking about.
7 And if you are interested, if you haven't made a
8 connection yet with FDA, look up the patient
9 representative program and reach out to one of our
10 colleagues in that office. There is a way to do it
11 that's explained on the website. Okay. We have one
12 person on the phone we'd like to -- Operator?

13 OPERATOR: If you'd like to make a comment
14 on the phone lines, your lines are now open.

15 JANE WOLFE: Yes, this is --

16 DR. EGGERS: Hello.

17 JOYCE WOLFE: Hello?

18 DR. EGGERS: Yes, good morning.

19 JOYCE WOLFE: Hello?

20 DR. EGGERS: Hello, we can hear you.

21 JOYCE WOLFE: Thank you. This is Joyce
22 Wolfe. I am the mother of two sons with Zellweger

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

182

1 syndrome. They basically have liver disease, adrenal
2 insufficiencies, deaf-blindness, myelin abnormalities
3 and delay seizures, muscle weakness, cognitive issues,
4 behavior and sleep problems, bowel and bladder control
5 issues, balance and walking problems. My sons were
6 given six months to live and there's no cure.

7 The clinical trials that we're involved in
8 in the U.S. are the cholic acid for bile acid
9 deficiency. And in Europe, the DHA, ethyl ester for
10 the DHA deficiency. The cholic acid trial in the
11 United States was quite easy and well managed and we
12 had no problems with compliance. The Europe trial, we
13 made 18 trips to Europe until the research physician
14 passed away. And when we were unable to give the DHA
15 ethyl ester, we saw a drop in the plasmalogens and
16 increase in liver enzyme function tests, regression in
17 physical performance, weight loss and inability to
18 absorb fat-soluble vitamins, increase in irritability,
19 decrease in appetite and increase in (inaudible)
20 seizures.

21 The DHA is not available in the United
22 States but it should be since our children have

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

183

1 difficulty breaking down our common type glycerides
2 from DHA. And the research that was done abroad shows
3 remarkable benefits and improvement in liver function,
4 myelination, vision, muscle tone and overall health.

5 The questions that I would put out, my
6 children, if they wanted to be involved in a clinical
7 trial, is they are both so anxious to be well, to have
8 lives that are not affected by deaf-blindness and poor
9 muscle control and deterioration in their condition,
10 that they would do anything to -- that showed a small
11 amount of hope for them to continue to live a
12 profitable life.

13 And I really agree with the comment that was
14 made that our children are dying, and we need the kind
15 of help that is already out there to be brought to the
16 United States and to use what we have in the United
17 States as well to have it through the FDA to be
18 available for the treatment for all other children
19 that will come along, and to be treated as soon as
20 possible. Thank you so much.

21 DR. EGGERS: Thank you. And what was your
22 name again?

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

184

1 JOYCE WOLFE: Joyce Wolfe.

2 DR. EGGERS: Joyce. Thank you, Joyce.

3 Well, we are to the end of our time for this
4 discussion. Of course, it could keep going. There
5 are so many other things to talk about. We didn't get
6 to touch upon challenges in eligibility criteria, for
7 example, for those of you that wanted to participate
8 in trials and haven't been able to, or in other issues
9 such as awareness, or other issues related to clinical
10 trials, or the other treatments that you're taking.
11 Again, we have the docket and we really encourage you
12 to contribute to the docket.

13 With that, I'm going to turn this over to
14 Pujita who is going to do the open public comment.

15 DR. VAIDYA: Hello, everyone. I'd like to
16 thank you all for coming today. We are now moving
17 into the open public comment session, and for those of
18 you who are not aware, the purpose of this session is
19 to allow an opportunity for those who have not had a
20 chance to speak on issues that are not related to our
21 two main discussion topics. This is an opportunity
22 for folks who are not patients or patient

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

185

1 representatives to comment.

2 Please keep in mind that we will not be
3 responding to your comments but they will be
4 transcribed and be part of the public record since we
5 would like this to be a transparent process. We
6 encourage you to note any financial interest that you
7 have that are related to your comment. If you do not
8 have such interest, you may state that for the record.
9 And if you prefer not to provide this information, you
10 can still provide your comments.

11 So we have collected signups before the
12 meeting and during the break in the interest of time.
13 We have about six -- we have six people signed up for
14 this session, so please be respectful for your other
15 colleagues here and other patients and stick to the
16 two to three limit that we have. We won't have a
17 timer but I will be keeping track of time. So if you
18 approach the two to three minutes, I will ask you to
19 start wrapping up.

20 So I'll quickly run through the order of
21 speakers and I apologize if I mispronounce your name.
22 We have first, Austin Noll; second, Page Migliozi;

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

186

1 Eduardo Balcells; Cristy Balcells; William Nyhan; and
2 Jana Monaco. So could we please have Austin Noll to
3 the mic, please?

4 AUSTIN NOLL: I've pulled it together. Just
5 a quick follow-up comment and it's on the safety
6 versus efficacy waiting. You need to think about that
7 because efficacy is inherently extremely difficult
8 with this patient population. You know, I can take 10
9 kids with Sanfilippo who are my son's age, they're all
10 going to be different. And my son is different every
11 day. So if you wait forever to figure out efficacy,
12 we got a huge problem. You really need to take a look
13 at safety and then efficacy will come as we get
14 things out. Thanks.

15 DR. VAIDYA: Thank you, Austin. Next, could
16 we have Paige?

17 PAIGE MIGLIOZZII: Hi. My name's Paige
18 Migliozi. My son, Christopher, had MPS I Hurler
19 syndrome.

20 Last night, my 8-year-old daughter cried in
21 my arms putting herself to sleep because her brother
22 died 10 years ago tomorrow from Hurler syndrome. So

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

187

1 tomorrow marks a whole decade of my life that I have
2 been without my son.

3 My 7-year-old son, when he goes to school
4 and they talk about superheroes, he comes home and
5 says, mamma, I wish I could be a superhero so I could
6 undead my brother and so he could come and play with
7 me.

8 I want you all to know the work you do is so
9 important. There are families out there. There are
10 real people who need your help and need your cure.
11 Christopher was one of the first people to undergo
12 enzyme replacement therapy in addition to chemotherapy
13 and transplant. And we've talked about transplants
14 and transplants have a lot of problems. They're not
15 to be taken lightly, and he died of post transplant
16 complications. I only had him for 14 months but I've
17 spent the past 10 years grieving his death.

18 So on behalf of me and my family, I want you
19 to know we need you because we need hope. These kids
20 are running against an invisible clock. We all are.
21 So thank you for all the work that you do and
22 remember, we need you. We need that hope for our

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

188

1 children. Thank you.

2 DR. VAIDYA: Thank you, Paige. Next, we
3 have Eduardo.

4 EDUARDO BALCELLS: Thank you again for the
5 opportunity to participate in this wonderful event.
6 Again, my daughter has mitochondrial disease, Leigh's
7 disease specifically. She's our youngest daughter.
8 My background, I'm a physician so one of the things
9 that I go through that's striking for me is that in my
10 world of patient care, I have a list of -- my patients
11 come in and they have a list of medications they're
12 on, on the average of 8 to 12. In my daughter's case,
13 she has no proven therapies, no proven treatments.

14 Some comments on some of the previous
15 comments made this -- during the previous discussion.
16 It's important for us to realize that without opening
17 up the access to a patient's four studies that we, as
18 parents, have to resort to unproven therapies,
19 anecdotal treatment and that carries risk in and of
20 itself.

21 So for my daughter, she's on a host of
22 compounded pharmacy vitamins, cofactors which are

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

189

1 compounded. But again, that's not regulated. I don't
2 know exactly what she's getting. We believe it's
3 helping her so -- but we are resorting to anecdotal
4 care. And it's striking to me that, you know, in many
5 of the adult chronic conditions, we do a very good job
6 with our studies and patients have choices. So there
7 are five different types of hypertensive medications
8 or cholesterol medications. And again, in our space,
9 we have no therapies.

10 So I would ask that we -- when we look at
11 our children and adults with these types of diseases
12 that we maybe perhaps look at it through a different
13 lense. and as was mentioned before, safety is key but
14 perhaps that risk is with not a "capital R" but a
15 "small r" because really, without anything to offer
16 our kids, again, we're left to anecdotal care, and
17 that's a difficult situation to be in. So, thank you.

18 DR. VAIDYA: Thank you, Eduardo. Next, we
19 have Cristy.

20 CRISTY BALCELLS: I also wanted to thank
21 NORD, the National Organization for Rare Diseases for
22 having us here today because we would not have known

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

190

1 about this meeting had it not been for them and their
2 support.

3 Again, my name is Cristy. I'm the Executive
4 Director of MitoAction which is a national
5 mitochondrial disease organization, and I'll speak as
6 a mother as well as a national patient advocate in
7 saying that the inclusion criteria and the end points
8 which make for good published data don't really matter
9 to us.

10 What matters to us is what you heard today.
11 What matters to us is if my daughter is so shaky that
12 I have to sit and feed her every bit of her yogurt or
13 if she can feed herself. What matters to us is
14 whether our kids are able to sleep through the night
15 so that all of -- everybody in the family can have a
16 little bit of peace. What matters to us is whether we
17 feel like we're at the doctor every week or if we're
18 at the doctor every couple of months. These things
19 have huge impacts on our quality of life but they
20 don't make good, publishable graphs, right. But they
21 make real differences in the lives of our kids and in
22 the lives of those that we love that have this

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

191

1 disease.

2 The second thing that I would say is that I
3 would not have known about this meeting, and will
4 certainly pay much more attention to the patient voice
5 opportunities within the FDA, had it not been for
6 NORD. But as the Director of a national organization,
7 please, FDA, reach out to us. We're coming to you
8 with these comments but certainly, I feel that any of
9 us who are here today representing patient advocacy
10 groups would jump at the chance to have our comments
11 be heard. So please, find us. We are all using
12 social media so it's actually pretty easy to -- for
13 our patients to find us when they're facing that
14 diagnosis. I believe that you could also and we
15 really want that opportunity to share our voice.
16 Thank you.

17 DR. VAIDYA: Thank you, Cristy. Next, we
18 have William Nyhan.

19 DR. WILLIAM NYHAN: Yes. I'm a little
20 different. I'm a physician, professor of pediatrics
21 at the University of California. I've been around,
22 I'm happy to say, long enough so that I've witnessed

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

192

1 the initial description of most of the diseases we're
2 talking about here and certainly all of the ones that
3 have been defined on an enzymatic basis and, in fact,
4 a handful of those, we've been the people that found
5 those defects.

6 I'm really delighted with what we've known
7 to have accomplished so far but I think that there
8 also is a future. I mean I don't think that there is
9 going to be more in the terms of dietary restriction.
10 I think we probably know as much as we're going to
11 know about that. But I think there are new and
12 different drug possibilities along the line.

13 Among them, I'd like to point out the
14 development of nitisinone. That came from a biochemist
15 in Canada who was studying this stuff that was
16 developed as a rat poison, and he found the enzyme
17 that it inhibited, and as soon as we knew what enzyme
18 that was, it became apparent that this was a treatment
19 for tyrosinemia which was killing kids and destroying
20 their brains very largely in Canada but throughout the
21 United States and the world. Now that's an effective
22 treatment and we've also discovered an even more

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

193

1 effective treatment for alkaptonuria, a crippling
2 disease of adults.

3 Finally, I would say that in terms of
4 clinical pharmacology and the study of the mechanism
5 of drug action, we're beginning to learn that drugs,
6 even those already on the market, are having effects
7 on areas of metabolism that point out that they may,
8 in fact, be effective treatments for a particular
9 disease. And so I'm hopeful that there is going to be
10 more of that.

11 DR. VAIDYA: Thank you, William. And
12 lastly, we have Jana Monaco.

13 JANA MONACO: Hi. Again, I'm the Advocacy
14 Liaison with the Organic Acidemia Association and
15 we, those of us who are parents with these children
16 and young adults living with these disorders, like the
17 other mom, I -- our anniversary was 13 years ago last
18 week that my son was diagnosed with his disorder,
19 isovaleric acidemia. And when you look at your child,
20 any of us know that if you look at your child who is
21 in a coma, on life support, who was running around
22 playing with toys the day before or has slowly

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

194

1 deteriorated over time with -- for unknown reasons,
2 you almost are willing to do anything and everything
3 because you have nothing else to lose.

4 And so in the 13 years that we have been
5 dealing with life after my son's diagnosis, I have
6 been with families who have shared similar stories,
7 who have lost their children, and some of us have
8 learned. And through, for example, children like my
9 daughter who came along a year after my son, because
10 of what we knew, they are perfect examples of the pros
11 and cons and what education does for rare diseases and
12 these IEMs and what can be done.

13 And research prior to his diagnosis has
14 helped many along the way and there are far less
15 children and young adults living with the severe
16 disabilities that my son, Steven, has and more
17 thriving like my daughter, Caroline. And it is the
18 effective treatment that they are on and the studies
19 that have been done to look at that, and they've doing
20 well.

21 However, for those of us with IEMs, know
22 that the very medical foods and formulas and

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

195

1 supplements aren't even really recognized yet as true
2 treatments to even get that authorization to be funded
3 for. So families suffer, they struggle to have access
4 to it and the funding for it, and they will
5 compromise, unfortunately, sometimes. So we need to
6 be able to address what's right there before our eyes
7 and get that -- these medical foods and formulas are
8 the elephant in the room and no one seems to be able
9 to move them beyond stagnation and know what to do
10 with it in healthcare reform.

11 And last but not least, my children are in a
12 few different studies right now at NIH and at
13 Children's National to study these disorders a little
14 bit more in understanding how they affect them
15 nutritionally and for immune sensitivities and so
16 forth because the fact that we know that they are
17 lifelong and we have to look beyond the early
18 diagnosis years and how these disorders affect them
19 throughout their life cycle.

20 And as far as consent, my daughter, who is
21 11, is part of the decision to participate in these
22 research studies because she knows she does not want

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

196

1 to get sick like her brother, and he is a constant
2 daily reminder to her of what can happen if it doesn't
3 take place.

4 So thank you for your support in these
5 conditions.

6 DR. VAIDYA: Thank you, Jana. Thank you,
7 everyone, and I would like to quickly remind you to
8 pass your clickers to the end of the rows and we'll
9 ask some FDA folks to pick it up.

10 And now I would like to call Dr. Teresa
11 Buracchio to the stand for our closing.

12 DR. BURACCHIO: So I would like to just
13 start by thanking all of the patients and families who
14 came today. I know many of you traveled long
15 distances to come here. We are very grateful that you
16 were willing to share your experiences and your
17 stories with us. They're very moving and we're taking
18 it all to heart.

19 So just to summarize what we heard today.
20 In our first topic, we talked a bit broadly about the
21 different types of neurologic symptoms that many of
22 you are experiencing. I think one of the things that

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

197

1 came up is one of the most distressing symptoms was
2 loss of language and being non-verbal. We hear that
3 the frustration with the inability to communicate may,
4 in fact, lead to some of behavioral problems that
5 you're seeing and that there is great frustration on
6 both sides with inability to express pain that the
7 patient might be having or any distress that they
8 might be experiencing. And of course, we understand
9 that there is great heartbreak at no longer being able
10 to hear your child's voice.

11 Other things that came up as being quite
12 important are, of course, cognition. I think that
13 wasn't too much of a surprise. We knew that that is a
14 widespread problem across all of these diseases. And
15 particularly, this discussion of executive function
16 came up.

17 And then the challenges with dealing with
18 troubling behaviors, things like impulsivity and
19 aggression and some socially inappropriate behaviors,
20 but just really, the main goal with those behaviors is
21 that you want your children to be safe and not engage
22 in unsafe behaviors and that, you know, ideally want

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

198

1 to be able to do the daily tasks that you need to do
2 like go to the store.

3 I think one of the new things for me hearing
4 today was some of the psychiatric symptoms, that
5 anxiety came up several times. Also, the symptom of
6 psychosis with delusions and hallucinations was a new
7 one for me to hear about. And this idea of emotional
8 regulation, that the children can go from laughing to
9 crying pretty quickly. I saw a lot of nodding heads
10 to that particular symptom. And sleep, insomnia or
11 night terrors or sleep walking.

12 We want to encourage you to continue to tell
13 us -- more people who didn't get to speak today or
14 people who are on the phone, do go to that docket and
15 enter, you know, greater -- you know, we covered a lot
16 of these broadly and we didn't get to dig too deeply,
17 so please go back, write it out, send it in to us. We
18 want to hear more.

19 And the second -- and then I should also
20 mention that there was a really great question that
21 came up with we're hearing all these symptoms, so how
22 do we measure these things. And that is a problem

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

199

1 that we all struggle with. You know, there are some
2 scales that exist for some of these but they haven't
3 really been used in these populations per se. But I
4 think the first step into developing these scales is
5 to know what the problems are in the first place, so
6 we made some important first steps here today to get
7 to that point where we can develop some scales to
8 hopefully capture some of these symptoms.

9 In the second part of our discussion today,
10 we touched on the therapies that are available and
11 what different people's experiences have been with
12 those therapies. I think we can all agree that the
13 therapies are limited and there needs to be more
14 options.

15 I think there is general consensus that you
16 want the opportunities to be involved in clinical
17 trials and that you are willing to take on some risks
18 although those risks will vary for individuals and
19 also depends on, you know, therapies that may be
20 available for the disease.

21 But overall, I think we had a great
22 discussion today. It was a very informative, very

Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014

200

1 productive talk.

2 So I'd like to just wrap up with some
3 additional thank yous. So once again, thank you to
4 all the families who participated and thank you to
5 everyone else who participated either by phone or in
6 person. I want to also thank the organizers of
7 this -- Sara Eggers and Pujita Vaidya did a great job
8 of organizing this -- and the support of our division
9 leadership with Donna Griebel, Andrew Muhlberg who
10 couldn't be here today but was very invested in this,
11 Julie Beitz, and Amy Edgan. And also, thank you to
12 NORD. I know that NORD provided transportation costs
13 for some of the people who were able to come here, so
14 thank you very much for that.

15 With that, I think we can end.

16 (Applause.)

17 DR. EGGERS: Thank you very much, Teresa.
18 And she has summed it up for all of us, I think, in
19 her thank you and in her summary.

20 I just have one kind of business thing which
21 is if you haven't completed an evaluation form, we
22 would very much appreciate your thoughts on how the

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

201

1 meeting went today. It's a one-page form so if you
2 could fill it out and leave it for us.

3 And with that, well, thank you again for
4 traveling here and for being here with us and sharing
5 your experiences and perspectives. Thank you very
6 much.

7 (Whereupon, at 1:02 p.m., the meeting was
8 adjourned.)

9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

202

1 CERTIFICATE OF NOTARY PUBLIC

2 I, JEN METCALF, the officer before whom the
3 foregoing hearing was taken, do hereby certify that
4 the testimony appearing in the foregoing hearing was
5 taken by me in audio recording and thereafter reduced
6 to typewriting under my supervision; that said
7 transcription is a true record of the proceedings;
8 that I am neither counsel for, related to, nor
9 employed by any of the parties to the action in which
10 this deposition was taken; and, further, that I am not
11 a relative or employee of any counsel or attorney
12 employed by the parties hereto, nor financially or
13 otherwise interested in the outcome of this action.

14

15

16

17



18

JEN METCALF

19

Notary Public in and for the

20

STATE OF MARYLAND

21

22

**Capital Reporting Company
Inborn Errors of Metabolism Patient-Focused Drug
Development 06-10-2014**

203

1 CERTIFICATE OF TRANSCRIPTION

2

3 I, LUCY T. TURNBULL, hereby certify that I am not
4 the Court Reporter who reported the following
5 proceeding and that I have typed the transcript of
6 this proceeding using the Court Reporter's notes and
7 recordings. The foregoing/attached transcript is a
8 true, correct, and complete transcription of said
9 proceeding.

10

11

12 June 24, 2014

13 Date

14

15

16

17

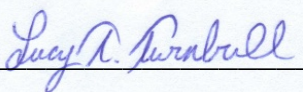
18

19

20

21

22



LUCY T. TURNBULL, CET

Transcriptionist