FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING (CRDAC)

Thursday, October 10, 2024

8:15 a.m. to 5:45 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Javed Butler, MD, MPH, MBA

(Chairperson)

Distinguished Professor of Medicine

University of Mississippi

President, Baylor Scott and White Research Institute

Dallas, Texas

Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA

Professor of Medicine, Duke University

President and Executive Director

Inova Heart and Vascular Institute

Falls Church, Virginia

Eric Peterson, MD, MPH

Vice Provost, Senior Associate Dean and Professor

University of Texas Southwestern Medical Center

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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Narimon Honarpour, MD, PhD

(Industry Representative)

General Medicine Head & JAPAC

Global Development Head and Vice President

Thousands Oaks, California

TEMPORARY MEMBERS (Voting)

G. Caleb Alexander, MD, MS

Professor of Epidemiology and Medicine

Johns Hopkins Bloomberg School of Public Health

Baltimore, Maryland

Gerard T. Berry, MD

Professor of Pediatrics

Harvard Medical School

Medical Staff

Boston Children's Hospital

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Matthew Clark, MD

(Patient Representative)

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Perelman School of Medicine
University of Pennsylvania
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Tobias Gerhard, BSPharm, PhD

(via video conferencing platform)

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Director, Institute for Health, Health Care Policy and Aging Research
Director, Center for Pharmacoepidemiology and Treatment Science
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Associate Professor, Epidemiology

Director, Center for Pharmacoepidemiology

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

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Division Chief of Medical Genetics

Medical Director, YT and Alice Chen Pediatrics

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CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:15 a.m.)

Call to Order

Introduction of Committee

DR. BUTLER: Good morning, and welcome. It's 8:15, and we will start the meeting. I would first like to remind everyone to please mute your line if you're not speaking, and also a reminder to everyone, please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email is currently displayed.

My name is Dr. Javed Butler, and I will be chairing this meeting. I will now call the October 10, 2024 Cardiovascular and Renal Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to the left and go around the table.

DR. CAVAZZONI: Good morning. I am Patrizia

Cavazzoni. I am the CDER Center Director.

DR. STEIN: Good morning. I'm Peter Stein, Director of the Office of New Drugs, CDER, FDA.

DR. JOFFE: Good morning. I'm Hylton Joffe, Director of the Office of Cardiology, Hematology, Endocrinology, and Nephrology in CDER, FDA.

DR. GANDOTRA: Good morning. I'm Charu Gandotra, Clinical Team Leader from Division of Cardiology and Nephrology, CDER, FDA.

DR. PUNNOOSE: Good morning. I'm Ann Punnoose, Clinical Reviewer in the Division of Cardiology and Nephrology.

DR. BAI: Good morning. I'm Steven Bai. I'm a statistical reviewer at the Office of Biostat at FDA.

CDR BONNER: We will now start with our virtual participants, starting with Ms. Shuman. Please state your name and your affiliation.

MS. SHUMAN: Hi. My name is Devin Shuman. I am the acting consumer representative, genetic counselor, Genetic Support Foundation in Bellevue, Washington.

CDR BONNER: Thank you.

Next is Dr. Kishnani.

DR. KISHNANI: Hi. I'm Priya Kishnani. I'm Division Chief for Medical Genetics, Duke University Medical Center.

CDR BONNER: Thank you, ma'am.

Next is Dr. Gerhard.

DR. GERHARD: Tobias Gerhard, Director of the Institute for Health, Health Care Policy and Aging Research at Rutgers University.

CDR BONNER: Thank you.

Next, we have Dr. Jonsson-Funk.

DR. JONSSON-FUNK: Hello. Michele Jonsson-Funk. I'm an associate professor at the University of North Carolina in Chapel Hill, where I direct the Center for Pharmacoepidemiology.

CDR BONNER: We will now continue on with our in-person panel members.

DR. LePICHON: Good morning. My name is J.B. LePichon. I'm a child neurologist at Children's Mercy Hospital in Kansas City.

DR. SHAW: Hello. I'm Pamela Shaw. I am a

biostatistics investigator at Kaiser Permanente Washington Health Research Institute in Seattle.

DR. ALEXANDER: Caleb Alexander, Johns Hopkins, Professor of Epidemiology and Medicine.

DR. O'CONNOR: Good morning. I'm Chris O'Connor. I'm President of the Inova Schar Heart and Vascular Institute and a heart failure cardiologist in Fairfax, Northern Virginia.

CDR BONNER: Good morning. I am LaToya Bonner, DFO, DACCM.

DR. BUTLER: Good morning. Javed Butler. I'm a cardiologist at Baylor Scott and White Health in Dallas and Professor of Medicine at University of Mississippi.

DR. PETERSON: Good morning. Eric Peterson, cardiologist and Vice Provost for clinical Research, UT Southwestern.

DR. CLARK: Good morning. My name is Matt Clark. I'm a father of a patient with Barth syndrome, and I'm a pediatric cardiac intensivist at Children's of Alabama.

DR. ELLENBERG: Good morning. I'm Susan

Ellenberg, Professor Emerita of Biostatistics, Medical Ethics and Health Policy at Perelman School of Medicine, University of Pennsylvania.

DR. JOHNSON: Good morning. Jonathan Johnson, Professor of Pediatrics at Mayo Clinic in Minnesota, and I'm a pediatric heart failure and heart transplant cardiologist.

DR. BERRY: Good morning. I'm Gerard Berry. I'm a biochemical geneticist at Boston Children's Hospital and professor at Harvard Medical School.

DR. SOSLOW: Good morning. Jonathan Soslow. I'm a pediatric cardiologist at Vanderbilt. I direct our cardiac MRI program and co-direct our muscular dystrophy clinic.

DR. TUCKER: Good morning. Carole Tucker. I'm Professor, Chair, and Associate Dean of Research at University of Texas Medical Branch, where I direct the Center for Health Promotion, Performance, and Rehab Research.

DR. HONARPOUR: Good morning. I'm Narimon Honarpour, Head of Clinical development at Amgen, representing industry today. Thank you.

DR. BUTLER: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the

meeting topic during breaks or lunch. Thank you.

Commander Bonner will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and

temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application, NDA, 215244 for elamipretide hydrochloride injection, submitted by Stealth BioTherapeutics, Incorporated, for the treatment of Barth syndrome. This is a particular matters meeting during which specific matters related to Stealth BioTherapeutics' NDA can be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Narimon Honarpour is participating in this meeting as a non-voting industry representative

acting on behalf of regulated industry. Dr. Honarpour's role at this meeting is to represent industry in general and not any particular company. Dr. Honarpour is employed by Amgen.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal and imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BUTLER: Thank you.

We will now proceed with the FDA's introductory remarks from Dr. Hylton Joffe.

FDA Introductory Remarks - Hylton Joffe

DR. JOFFE: Good morning, everybody. My name is Hylton Joffe. I'm the Director of the Office of Cardiology, Hematology, Endocrinology,

and Nephrology at FDA. I'd like to welcome you all here today, where we'll be discussing elamipretide for the treatment of Barth syndrome, and I look forward to today's discussion. What I'd like to do in the next 10 minutes or so is provide some information that I think the advisory committee will find useful as you hear the presentations this morning and as you deliberate on the issues.

So a brief word about Barth syndrome and elamipretide, and of course you're going to hear a lot more about these over the course of the day, Barth syndrome is a rare, serious mitochondrial disease caused by mutation of tafazzin, and tafazzin is needed for maturation of cardiolipin, which is a phospholipid in the mitochondrial membrane that has a critical role in mitochondrial shape and ATP production.

People with Barth syndrome have a variety of manifestations, including fatigue, skeletal myopathy, heart failure, neutropenia, among others, and also suffer from premature death. Currently, treatment is supportive -- for example, standard

heart failure therapies -- and there are no therapies that are specifically approved for Barth syndrome.

The applicant proposes that elamipretide causes aggregation of cardiolipin, improving lipid packing in the inner mitochondrial membrane that then improves the structure and the function of the energy-generating proteins in the mitochondria, and today you'll be hearing about efficacy data from the studies shown on this slide.

SPIBA-201 Part 1 was a randomized, double-blind, placebo-controlled crossover trial; SPIBA-201 Part 2 was a long-term, single-arm, open-label extension, where patients got elamipretide after finishing Part 1; and then you'll hear about SPIBA-001, which is an externally-controlled study comparing patients who got elamipretide in SPIBA-201 to an external control. You'll also hear about other supportive data such as nonclinical studies, and the efficacy endpoints in these clinical studies included functional outcomes like the 6-minute walk test;

fatigue; echocardiogram parameters; and cardiolipin ratios.

The focus of today's advisory committee meeting is, can we conclude that elamipretide is effective for the treatment of Barth syndrome based on the available evidence? The advisory committee is going to hear differing perspectives on the answer to that question from the applicant and from the FDA review team, and we ask the advisory committee to consider these two perspectives and to provide your independent expert advice and recommendations based on the available evidence.

I'd now like to take a few minutes and cover some background that I think will be helpful for the advisory committee as you hear the presentations today, and I want to talk about our regulatory standard for establishing effectiveness, what we call substantial evidence of effectiveness.

A drug's effectiveness must be established before approval, and that must be based on what we call substantial evidence. Substantial evidence generally requires at least two adequate and

well-controlled clinical investigations that are each convincing on their own, but there are situations where FDA can also determine that data from one adequate and well-controlled clinical investigation, together with what we call confirmatory evidence that those together can constitute substantial evidence in lieu of a second adequate and well-controlled investigation. Within this framework, FDA can exercise regulatory flexibility.

What do I mean by an adequate and well-controlled investigation, what do I mean by confirmatory evidence, and what do I mean by regulatory flexibility? I'd like to take a moment and walk through each of those topics.

An adequate and well-controlled investigation provides the primary basis for determining whether there is substantial evidence, and these types of investigations have certain characteristics that help us distinguish an effect of the drug from other influences such as bias and changes in the disease that's unrelated to the drug

or placebo effect.

I've shown these characteristics on this slide. There are things like having a clear statement of objectives and having a design that permits a valid comparison with the control. Now, it's important to note that it does not have to be a placebo control. For example, we can accept a historical control when appropriate. Subjects, of course, have to have the disease of interest being studied.

The method of assignment of subjects to the treatment group and the control group should minimize bias to assure that the two groups are comparable. There should be adequate measures to minimize bias on the part of subjects, observers, and data analysts. There should be methods of assessment of response, and we're talking about the efficacy endpoints here that are are well defined and reliable, and then analysis of study results should be adequate to assess the effects of the drug.

What about confirmatory evidence? Well,

this is data from one or more sources that substantiate the results of the one adequate and well-controlled investigation in lieu of having that second adequate and well-controlled investigation. The amount and quality of your confirmatory evidence depends, in part, on your adequate and well-controlled investigation. For example, if you have a less persuasive adequate and well-controlled investigation, that may require greater quantity and compelling confirmatory evidence.

Now, I've shown on this slide some examples of what FDA can accept as confirmatory evidence, for example, mechanistic evidence. For example, if the disease pathophysiology and the drug's mechanism are very well understood and the drug directly targets the major drivers of the pathophysiology, that could be a case where FDA could use mechanistic evidence as confirmatory evidence.

There may be cases where we can accept evidence from a relevant animal model. This

depends on how similar the animal model is to what happens in humans. Is the pathophysiology of the disease the same? Is the pharmacology of the drug the same? Does the model recapitulate what happens in humans so that you could say that the evidence of efficacy in the animal model reasonably supports clinical benefits in humans? Another example could be real-world evidence. Of course, this depends on the reliability, the relevance of the data source, the study design quality, appropriate statistical methods, and so forth.

Then we can also consider evidence from expanded access use. Now, expanded access is where patients who have a serious life-threatening disease with no other treatment options, and they don't qualify for a clinical trial, they could get access to an investigational drug to try to treat their disease. In that case, we don't usually typically get efficacy data of the type that we look for in clinical trials. That's said, if there was a sufficient quantity and quality of expanded access efficacy data that was highly persuasive,

that could be something we could consider as well.

Now, what about regulatory flexibility? Well, FDA can exercise regulatory flexibility regarding the kind and quantity of data required to meet our statutory standard of substantial evidence, and we consider things like disease severity, rarity, unmet need, or if there's feasibility or ethical issues. Examples of regulatory flexibility could include the type of study design, the number of studies or statistical considerations for concluding effectiveness, and so forth.

I've shown three examples here on the slide of regulatory flexibility. The first one is, if you have a rare disease where you barely have enough patients to do one adequate and well-controlled trial, a second adequate and well-controlled trial would be infeasible, and that would be a good case of using the approach of one adequate and well-controlled trial plus confirmatory evidence; or you may have a rare disease with so few patients that you can't fully

power a trial, and in that case, accepting a p-value that's higher than the typical 0.05 threshold may be acceptable but of course should be prespecified, appropriately justified, and discussed with the FDA.

A third example is FDA may accept a study design that produces less certainty, and that may be acceptable if a better study design is not feasible or not ethical. But it's important to underline all this by saying that in all cases, FDA has to conclude that there is substantial evidence of effectiveness, so that statutory standard of substantial evidence remains the same.

What I'd like to do is, just in a minute or two, walk through the discussion and voting questions so that the advisory committee can have these in mind as you hear the presentations. We have three discussion questions. The first one asks the committee to discuss whether SPIBA-201, Part 2 demonstrates that elamipretide is effective for the treatment of Barth syndrome, and we'd like the committee to include in your discussion the

interpretability of the single-arm, open-label study design and the findings on the endpoints that you'll hear about that are shown on this slide.

Question 2 asks the committee to discuss whether SPIBA-001 demonstrates that elamipretide is effective for the treatment of Barth syndrome. There again, we want you to include in your discussion interpretability of the study design, in this case, the externally controlled study, and then findings on these endpoints.

The third discussion question asks the committee to discuss the extent to which other data -- nonclinical data, other clinical study results -- support the effectiveness of elamipretide; and then after all that, we're going to ask the committee to vote on one question, which is shown here, which is, based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome?

Please provide the rationale for your vote. If you vote yes, specify the evidence of elamipretide's effectiveness, and if you voted no,

please provide recommendations for additional data that may support a conclusion that elamipretide is effective. That's the end of my presentation. Thanks for your attention. I'll turn it back to the chair.

DR. BUTLER: Thank you, Dr. Joffe.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with applicant, such as consulting fees, travel expenses, honoraria, and interest the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentation from Stealth BioTherapeutics.

Applicant Presentation - Reenie McCarthy

MS. McCARTHY: Good morning. My name is Reenie McCarthy. I am the Chief Executive Officer of Stealth BioTherapeutics. I'd like to thank the center leadership, Dr. Joffe, Dr. Gandotra, and the review team, to give us the opportunity, Dr. Butler and members of the committee, to share with you the data that we've generated over 10 years of development of elamipretide for the ultra-rare disease, Barth syndrome.

When patient advocacy first approached us in 2014 and asked us to initiate development, we thought we had a good idea of the challenges that would be entailed in developing a drug for disease this incredibly rare. I have to say, in

retrospect, that I think we severely underestimated the hurdles that we would face, but we've really persevered because we were inspired by the potential that we believe we've delivered upon to improve the lives of patients living with this serious rare disease. We look forward to sharing the data with you.

I'm here today with a number of my colleagues, as well as many experts in the care and treatment of Barth syndrome worldwide. We are eager to present our data to you and available to answer any questions that you may have.

So a little bit about Stealth, we are a very small, privately held, biotech company. We were founded based on the serendipitous discovery of a class of compounds that target the mitochondria, which was a previously undruggable target. With that, our mission is to develop therapies to treat serious diseases of mitochondrial dysfunction. This certainly includes Barth syndrome, but we are also in phase 3 clinical development in primary mitochondrial myopathy.

These diseases have a very high unmet medical need, so there are no approved therapies or, indeed, any therapies close to clinical development for Barth syndrome. There are no approved therapies for primary mitochondrial myopathy. There are no approved therapies for any genetic mitochondrial disease. I mention this because this has entailed a series of firsts, both for us as a developer and for FDA, in reviewing the evidence and the regulatory pathways.

Dr. Joffe mentioned Barth syndrome. I'll give you a little bit more detail. It is ultra rare, progressively debilitating, and fatal; ultra rare in that it affects about 130 boys and young men living in the U.S. The progressive skeletal myopathy, which results in truly crushing fatigue, debilitating exercise intolerance, and muscle weakness, is what patients point to as the most problematic symptom, impacting all aspects of their daily lives; so that did inform some of the endpoint selection in our development efforts.

Cardiomyopathy is both progressive and

evolving, and in all cases due to a severe, really severe, energy deficit in the heart. We can see evolution to a hypertrophic-like phenotype in periods of relative stability which can quickly decompensate into a more dilated phenotype, often precipitating an acute event. Lifespan is significantly reduced with 50 percent of deaths occurring by age 1. Puberty, which we studied in our trial, is an incredibly high-risk period due to the metabolic demands of growth, and most survivors of childhood do not survive their fourth decade.

Elamipretide, as I mentioned, was serendipitously discovered by researchers at Weill Cornell who were targeting receptors in the brain, mistakenly dosed a rat in the hind's limb instead of intrathecally, and radiolabeled the compounds when they found activity, determining that they were reaching the mitochondria where they interact with cardiolipin, as Dr. Joffe mentioned, to stabilize mitochondrial membrane structure and function. You're going to hear a lot more about cardiolipin today.

In terms of elamipretide for the treatment of Barth syndrome, we're dosing this as a once-daily subcutaneous injection. Barth syndrome is a very, very small patient population, but we do have safety from a broader database of patients with genetic mitochondrial diseases, as well as more common diseases; so overall, we've well characterized the safety profile with over 400 patient-years of exposure.

The severe bioenergetic deficit in Barth syndrome is crucial to understanding the disease, it's crucial to understanding elamipretide's potential to improve signs and symptoms of the disease, and it's also important for understanding some of the concerns that have been put before you today regarding the potential impact and durability of effort bias over a long period of time in patients living with this disease. So if you'll bear with me, I'm going to give you a little mitochondria 101 refresher.

Mitochondria are essential for human life. They produce 90 percent of the energy that we need

to survive. This is particularly important for high-energy demanding organ systems like the heart and the skeletal muscle. Cardiolipin, which you can see pictured to the upper right, is essential for normal mitochondrial structure and function. It's a conically shaped phospholipid, so when we pack that together in the inner membrane, it drives the membrane curvature that you're seeing on the upper right-hand side of your screen.

If you drop your gaze down, we can see why that curvature is so important. The membrane curves called cristae cradle the complexes of the electron transport chain, maximizing the efficiency of energy production and minimizing leakage of a toxic byproduct, reactive oxygen species. Cardiolipin is actually embedded within and important for assembling the complexes of the electron transport chain. And with that, when it is embedded within these complexes, those have a protective effect on cardiolipin itself, so in normal healthy tissue, it has a fairly long half-life. So cardiolipin is necessary for

essential mitochondrial structure and function, and with that, it's necessary for human life.

Barth syndrome is a disease of really severe cardiolipin deficiency. Patients living with Barth syndrome have only 5 to 30 percent normal levels of cardiolipin. Cardiolipin is made in the mitochondria, so if you look to the upper right, you see the immature precursor of normal cardiolipin, and it's called monolysocardiolipin, and a transacylase called tafazzin assembles the last piece of cardiolipin to make the conically shaped mature cardiolipin you see on the lower right of your screen.

In Barth syndrome, mutations in the gene tafazzin cause a severe deficit in the transacylase tafazzin, leading to elevations of immature monolysocardiolipin called MLCL. The 70 to 95 percent deficit in mature cardiolipin, again, is essential to human life, so that deficit can be lethal. And not only do patients living with Barth syndrome have very low levels of conserved normal cardiolipin, but it's really rapidly chewed up by

reactive oxygen species in the setting of raging mitochondrial dysfunction. So as a result, we have mitochondrial dysfunction and signs and symptoms of this disease, which can actually be diagnosed by the ratio of abnormal MLCL to CL.

Elamipretide, as Dr. Joffe mentioned, interacts with cardiolipin, both cardiolipin and monolysocardiolipin, so cardiolipin in the inner membrane to improve that lipid packing, which drives membrane curvature. It can compensate for up to 30 to 50 percent levels of cardiolipin deficit across models, and it improves mitochondrial function within hours in explanted human heart tissue, and Dr. Chatfield, who's here with us today, has published on this.

Our theory was that elamipretide may normalize cardiolipin half-life, which again is about 75 percent reduced in Barth syndrome, by decreasing reactive oxygen species and improving the electron transport chain protein complex association, which is then protective of the embedded cardiolipin.

We have seen improved MLCL-CL ratios, as well as improved cardiolipin levels across preclinical models of aging heart failure, HFrEF, HFpEF, and in patients with Barth syndrome, we have also seen improvement in these ratios and in the levels of cardiolipin. Across models, we've seen improved cardiac function and muscle function.

This is a cross section of mitochondria, and on the left you can see in a healthy mouse heart that the striations are really showing you that curvature of the inner membrane. In the middle is the mouse model of Barth syndrome, and you can see that that membrane architecture is absolutely gutted.

With elamipretide over to the right, we see a trend towards normalization of mitochondrial ultra structure in this Barth syndrome model. That is associated in this model with improvements in mitochondrial respiration, which can also be measured in live cells, which is what I'm showing you here. So this is really measuring mitochondrial respiration or energy production in

Barth syndrome, patient-derived cardiomyocytes.

What you can see on the left, in brown, is that Barth syndrome cardiomyocytes are working very, very inefficiently in a resting state, much higher than normal, which is shown in blue or in green. Elamipretide, in red, can rescue that to some extent. In the middle during maximal respiration, which is necessary because our mitochondria literally make energy on demand to fuel heart or muscle function, you can see that Barth syndrome cardiomyocytes, in brown, can barely work any harder than they can at rest.

Again, elamipretide is raising that mitochondrial respiration rate closer to normal. At a cellular level, this is one of the reasons why experts find it improbable that effort bias alone could contribute to sustained functional improvements over a 4-year period in patients. The cells just don't work that way in this disease.

Our development efforts began in 2014. This has been the first and largest development effort ever undertaken for Barth syndrome. It has

involved about half of all evaluable U.S. patients. All aspects of trial design, including endpoint selection, were closely informed by both expert clinicians and by interactions with the FDA, including in the context of our sister program in primary mitochondrial myopathy.

When we read out on the TAZPOWER in 2018, which the crossover trial did not show benefit in 3 months of treatment, our belief was that we had not treated for long enough, and our concern was that we had already utilized most or all of the eligible U.S. patients in that trial. There was a competing clinical development effort at the time ongoing in Europe, which was the second largest cohort of patients worldwide. That effort ultimately failed, but with that, in early 2019, we turned to the substantial evidence guidance that the FDA had put forth to try to maximize the interpretability of our open-label data which had just started. That is really what led to us establishing an external control for the TAZPOWER extension data and what we're calling our natural

history control study.

Over the ensuing 5 years, we've met about 20 times with the FDA to discuss this program, and no other trial designs that had been discussed, including the randomized withdrawal trial mentioned in the FDA's briefing book, were ultimately acceptable to FDA, primarily due to powering concerns that are, frankly, insurmountable in a disease this rare.

When the FDA filed the NDA for elamipretide for the treatment of Barth syndrome, it was on the basis of our position that traditional or full approval should be supportable based on the adequate and well-controlled clinical trial, our natural history control study. You can see from the guidance, and also Dr. Joffe's remarks, that in special circumstances, including when it may be impractical or unethical, a well-designed natural history study can provide an external control group.

Now, the guidance explicitly rightly recognizes that bias can be a problem with these

designs. In the guidance, it says that if the drug effect is large enough, it can overcome some of these concerns of bias, as well as a number of other statistical and design considerations that we really did take into account in constructing what was a very rigorous natural history control study. There have been many therapies approved by the FDA recently utilizing external controls.

The other pathway that we did discuss with the agency at some length was Subpart H accelerated approval, which the FDA is required to consider in situations of serious rare diseases, where experts could reasonably conclude, based on biomarker findings like the MLCL-CL ratios or echocardiographic parameters, that a drug like elamipretide is reasonably likely to have its predicted effect, and then sponsors are required to prove that again postmarketing. It's not required under Subpart H that surrogate and intermediate clinical endpoint data be generated in a randomized-controlled trial. FDA's concerns about powering the requisite postmarketing study

ultimately led to preclusion of consideration of this pathway.

This is my elephant-in-the-room slide. I'd like to try to crystallize a couple of the key questions before you today, setting aside some of the statistical concerns which are important, but I'm going to leave my colleagues, Dr. Carr and Dr. Wittes, to speak to. Two major questions that have been posed are whether the placebo effect, which was observed on a single endpoint of the 6-minute walk test, precludes interpretability of the entirety of this data package.

Just to speak to that briefly, there was no placebo effect observed in the TAZPOWER crossover trial on any of the other functional endpoints assessed. We really saw no movement on muscle strength, 5 times sit-to-stand, or balance, and we believe that those endpoints should remain interpretable, particularly compared to an external control. I will note that the 6-minute walk test was informed to the best of our knowledge at the time by expert advice from experts in Barth

syndrome, and it was recommended to us as the sole primary endpoint by the FDA in a related disease of primary mitochondrial myopathy being examined under the same IND.

I will also note that while I recognize the FDA's concern and agree that bias is an important topic for discussion, the data does not support that presumption of effort bias. The 30-meter placebo effect that was observed during the crossover trial was within the patients' prerandomization 6-minute walk test values. There was a dip between screening and baseline values for these patients, likely due to the exhaustion from frequent travel between those two assessments -- that we don't know -- but we do know that fatigue and recovery from activities is a huge issue in this disease. We do not think that the improvements observed can be pinned solely to effort bias here.

We note that the 30-meter placebo effect is within the variability seen in short-duration heart failure trials -- Dr. Udelson can speak to

that -- and we know that long-term therapy and open-label extension exceeded that placebo effect by 3 times, despite no increase in effort, reported by patients on the BORG assessment.

The second question is whether the totality of the evidence relative to the benefit-risk profile of elamipretide supports the finding of efficacy. I would just point out that we have data on multiple kinds of endpoints here. We have multiple lines of inquiry, multiple lines of assessment.

We've looked at several different functional assessments. We've looked at several assessments of how patients are feeling. We've looked at inherently objective endpoints like cardiac echocardiograms and the molecular cardiolipin ratios, which really are at the heart of this disease, and we see unidirectional improvement on elamipretide that's durable over a 4-year period and completely unpredicted in the natural history of this progressive disease. There have been no material safety concerns identified.

I'm not going to belabor this because Dr. Joffe covered it really well, but the statutory standards for an evaluation of efficacy do rest on investigations on the basis of which experts like yourselves could determine that a drug will have the effect it's represented to have, and Subpart E of Title 21 goes on to mandate the broadest flexibility, again as Dr. Joffe mentioned, in evaluating drugs for serious rare diseases that have no other approved therapies, and this specifically recognizes the benefit-risk analysis.

Finally, for those of you on this committee, I'm sure you will remember Dr. Stockbridge's comments in the setting of the Entresto adcom in 2020, which pointed to the legal language referring to information that experts would find compelling. We do have many experts with us here today who have contributed also to the public docket and will be speaking in the open public hearing, and I encourage you to take their comments into consideration.

When we plot the data on a forest plot to

really show whether we have consistency across all of the endpoints assessed, we can see on the left, relative to natural history controls, and on the right relative to patients' own baseline controls, that there's a concordance of the evidence, again, in how patients are functioning, how they are feeling, how their mitochondria are performing, and how their hearts are performing that favors elamipretide.

We, too, would like to know more about elamipretide in the setting of Barth syndrome, but with over 20 meetings and about a dozen different protocols discussed with the FDA over the years, we've concluded that postmarketing disease monitoring is the best way to understand whether elamipretide can improve outcomes for patients living with this disease, so we've committed to study on a postmarketing basis both patients prescribed with elamipretide treatment and on standard of care, not elamipretide, to assess long-term outcomes.

I'd like to leave you with a few thoughts on

the rationale for the approval of elamipretide. I would be remiss not to mention the urgent unmet need. This is a really severe debilitating disease with very high pediatric mortality. There are no other therapies approved and none close to clinical development. We've been seeing increasing demand from expanded access requests from a dozen U.S. hospitals and about 9 foreign countries. Many of these are for babies in acute cardiac distress. The FDA has approved every request put before it for emergency access.

The safety profile of elamipretide has been well characterized with over 400 patient-years of exposure, over 1700 patients exposed, and mild to moderate injection site reactions as the most common finding. The totality of the evidence has been assessed relative to about 50 percent of the evaluable U.S. patient population. We're seeing improvements in how mitochondria work in cells. The MLCL-CL ratio is improved significantly. Function has improved and that's been durable. Exercise tolerance, strength, and balance all

improved.

Patients are feeling better. These have been durable and large improvements reported by patients and the clinician, and patients have characterized these improvements in terms of what it means for them and their activities of daily living. Patients can work at jobs for the first time. Patients can go to school and stay for a full day or transfer between classes on their own. Recovering from activities has been reported, improved appetite, which is an issue in Barth syndrome, and the hearts are working more efficiently.

So with that, I'd like to introduce Kate McCurdy, the chair of the Barth Syndrome Foundation.

Applicant Presentation - Kate McCurdy

MS. McCURDY: Good morning. I'm Kate McCurdy, one of the founders of the Barth Syndrome Foundation, the only organization in the world that focuses on our ultra-rare mitochondrial disease, and I now serve as the Chair of the Board of

Directors. I'm here today as a volunteer, as I have been at all of the FDA-Stealth meetings that I've attended, and I've only had my travel expenses paid by Stealth. But my most important credential this morning is that I'm the mother of a wonderful son who's now deceased. So I've witnessed this devastating disease and the life-threatening disease not only side by side, every day with one patient throughout its entire life, but also through many conversations, testimonies, and visits with lots of other Barth families over the years. So today, I'll do my best to summarize the patient perspective.

I wanted to start by describing a little bit about my son's personal medical journey because he's a really good case study since, unfortunately, he endured all but one of the major complexities of Barth syndrome. The one thing he never experienced was a heart transplant. He was a bright, compassionate, and wise human being who contributed much to the world and to medicine despite his significantly compromised health and quality of

life; but these vibrant pictures of him can be very deceiving, as he lived with significantly compromised health and diminished quality of life. Under the blue shirt in this healthy looking photo on the right, you'll see what his abdomen and chest actually looked like in the photo on the left here. He had an internal defibrillator, a G-tube, and a port-a-cath, and his smile and demeanor belied just how ill and vulnerable he was all the time.

There's a lot on this slide, but I just want to summarize by saying that after experiencing some unusual gross motor aberrations early in life, Will suddenly ended up in the ICU in heart failure at age 2, and the possibility of a heart transplant was then discussed. He was diagnosed with cardiomyopathy and left ventricular noncompaction, and later at age 16, he had another episode of heart failure that took him back to the ICU.

He recovered slowly from both of these episodes well enough, with the help of the most up to date cardiac medications and protocols, to avoid transplant, but he was never very well and

certainly never robust. He suffered from cyclic neutropenia, which led to frequent neutrophil counts literally of zero, leading to many infections and healing problems. He, like many others, experienced serious cardiac arrhythmia, which led to the implantation of his internal defibrillator, and like almost all others with Barth syndrome, he had multiple GI and nutritional challenges, significant skeletal muscle weakness, absolutely crushing fatigue, which he described as just utter depletion of energy, and it took him a very long time to recover from that. He had severe exercise intolerance and a host of other clinical challenges.

On the right here, you'll see what all these issues led to: 47 inpatient hospitalizations leading to his spending more than a year and a half in the hospital during his life; 57 procedures under anesthesia, including multiple implanted defibrillators; lots of gastrostomies and ultimately their closures; many operations of various kinds, including those that were needed to

aid the healing of his scars. Every day he took 29 pills; 2 IV medications; 2 injection medications; TPN through his port-a-cath; and G-tube feedings overnight.

As I mentioned, the only procedure that's common among Barth patients that he did not endure was a heart transplant, though 16 percent of our cohort do have that procedure. He missed a great deal of school. One year, the 9th grade, he attended only part of a handful of days, and he died at age 28, which is heartbreakingly young. But he was one of the lucky ones who not only survived through infancy but also made it into his late 20s.

So before I go on, I just want to talk a little bit more about some background information about the Barth Syndrome Foundation itself, or BSF as we call it. We were founded by five parents in 2000, just four years after the causative single gene was discovered. We're headquartered in the United States, but we have four international affiliates, and together we comprise the only

patient group in the world for our ultra-rare disease.

Our mission is saving lives through education, advances in treatments, and finding a cure for Barth syndrome. We have a registry in which we collect both data and biological specimens on those with Barth syndrome, and we've got a human 2000 gene-variant database which is world renowned. We offer R&D, grant, and contract funding, and a number number of vital educational materials both for patients and their doctors, as well as some family support.

One of our signature events is our International Scientific, Medical, and Family Conference, which is held every two years, which includes one novel component that you're going to see in the photograph on the right here. What we try to do is to take advantage of the fact that we always seem to attract the largest groups ever convened of Barth patients at these meetings, certainly larger than any individual researcher could ever gather.

We set up various hotel conference rooms with different pieces of medical equipment and personnel we bring in, and we conduct several days of IRB-approved protocols, including various blood draws with local expert phlebotomists for a myriad of biochemical analyses. We do a broad array of data collection projects, utilizing things like echocardiograph machines, as you see in this photo.

It's really an amazing opportunity and one that's been used over the years by people like Dr. Hilary Vernon and her team, and you'll hear from her soon, to augment what data is collected through our two multidisciplinary clinics throughout the world and other specialized clinical studies, thus advancing the knowledge and the natural history understanding of our disease.

There are just over 300 individuals living with Barth syndrome in 37 countries around the world and only 129 in the United States, making Barth syndrome an ultra-rare disease clearly by any definition. Importantly, BSF has been in contact with over 90 percent of this global cohort, so our

reach is both broad and deep.

With this kind of clinical research history, what is our patients' perspective on drug development and on elamipretide specifically? Well, first and foremost, patients understand that they have a critical role in advancing medicine and have stated very clearly that they want a safe therapy to try, and we strongly believe that one is in front of you today. Even though the elamipretide trial officially ended in 2021, our community has either seen for themselves or heard from their friends that the trial participants who are still on drug have seen dramatic improvements that make meaningful differences in their daily lives. Most now go to school or work full time for the first time in their lives. That's transformational. Everyone has strength and stamina now to do regular chores of daily living that's allowed them to be more independent and allows more social interaction and a lot less isolation, which also is life altering. Recovery time from fatigue, as I mentioned, which is a real

problem, has been improved and has a real impact on the daily lives.

One specific aspect of how life has changed that I think is worth mentioning, because one can understand what a big difference it would make, is that two individuals in their mid-teens apparently experienced overnight bed-wetting before entering the trial, but both had that problem cease when they began taking elamipretide. That was a surprise and added benefit.

You'll hear more details about some expanded use cases in a bit in which the drug has made life-changing differences to very sick patients as young as newborns, and you'll also hear more specifics a bit later in the open public hearing part of this meeting from almost all of the patients who were in the initial trial or their caregivers. Only a few were not able to come today, but you'll hear from a lot of the people in the trial. I don't want to steal any of their thunder now, but I do know that you're going to hear a lot of corroboration about elamipretide's

life-changing potential from them.

So based on all of this, our community understandably is very eager to gain access to the drug for themselves; but it's not only patients who want the opportunity to try elamipretide. Nearly 50 distinguished and expert medical professionals have signed letters to the FDA in support of the elamipretide NDA for Barth syndrome because they've either seen the drug's benefit in a patient or have read about the trial results. This includes a large portion of the experts in the world and our ultra-rare disease and three physicians who've seen the vast majority of patients around the world, Dr. Peter Barth himself after whom the disease is named, as well as the heads of the two multidisciplinary Barth clinics around the world.

Even with all the positive data that have been generated about elamipretide's use in Barth syndrome, the necessarily extremely small trial size means that there remains some level of uncertainty about whether the drug might work well for all affected individuals, so several times our

patient community has directly addressed the FDA regarding their feelings about risks and benefits associated with therapy development. The first time was at our PFDD meeting in 2018, during which patients said that if there are no life-threatening side effects, they would try almost any treatment that would get to the root of the underlying problem of the syndrome and offer increased function and energy, as opposed to the therapies that are available now, which simply address one or more of the individual symptoms of the syndrome.

Then in 2021, we held a listening session with FDA to further explore Barth patients' thoughts about this issue of uncertainty of benefit, and we heard such things from patients such as living with Barth syndrome means facing constant uncertainty every day, as they know well that they can get very sick very suddenly, so uncertainty is no stranger to this population. They understand that universal clinical benefit is never guaranteed with any drug but they want to be able to try a drug that has at least a chance of a

benefit, and they say that Barth quality of life is so low that they need something soon. Patients and caregivers stated that they'd be willing to try a therapy that might improve quality of life even if the benefit is uncertain, and notably, even if it might come at the expense of prolonging life, and that is profound.

Since elamipretide development started in 2014, 18 percent of the Barth individuals in the U.S. have died and 12 percent of this cohort, an additional 12 percent, have required a heart transplant, so time is not on our side. Everyone who survives today lives every day with a life diminished by this horrible progressive disease, and as has been said, there are no approved therapies for this universally fatal disease and nothing else very far along in development.

So before I conclude, I want to help frame the impact of the advice you will render today by quoting Dr. Janet Woodcock, a former acting FDA commissioner, when she said, "Much of the effort in evaluating a drug development program goes to

avoiding a specific mistake; that is erroneously approving a drug that is not effective. There's often little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of those consequences are borne by patients who traditionally have very little say in how the standards are implemented." I ask that you keep that in mind today, please.

So please also remember that behind all the numbers and analyses you will see today are human beings. Barth syndrome patients and their families hope you will conclude that based on all the evidence, elamipretide is both safe and effective. To do so, I ask that you think hard about how best to make those determinations given the mathematical limitations that necessarily result from the very small number of patients who live with our extremely rare disease. The data, as well as what I personally have seen and heard from those who've taken this drug, have led me to be strongly

convinced that elamipretide can make a meaningful difference in the lives of those with Barth syndrome, and the time to give them access is now.

Thank you very much for listening and for including the patient perspective, and I now call Dr. Hilary Vernon to the podium.

Applicant Presentation - Hilary Vernon

DR. VERNON: Hello. My name is Hilary Vernon. Thank you for hearing me speak today. I'm a Professor of Genetic Medicine and Pediatrics at Johns Hopkins University School of Medicine. I also direct the Mitochondrial Medicine Center at Johns Hopkins, as well as founded and direct the Barth Syndrome Interdisciplinary Clinic at the Kennedy Krieger Institute.

A little bit of background about myself, I'm originally trained in biochemistry, University of Pennsylvania, and got my MD/PhD at Rutgers University in New Jersey. I completed combined residencies in pediatrics and clinical genetics at Johns Hopkins, as well as a fellowship in laboratory biochemical genetics at Johns Hopkins

University, and I'm board certified in pediatrics, clinical genetics, and clinical biochemical genetics. I joined the faculty at the Kennedy Krieger Institute in Johns Hopkins University in 2011, and I started the Barth Syndrome Clinic at Kennedy Krieger in 2012. My relevant disclosures are that I received research support from Stealth BioTherapeutics but have no other financial affiliations with them. I'm a member of the Barth Syndrome Foundation Scientific and Medical Advisory Board.

One of the big questions I often get when I tell people what my research and clinical focus is, is how did you get involved and focus on such an ultra-rare disease? I think like many things in research and academics, it was a very wonderful, serendipitous happening. When I came on to the faculty, another geneticist was retiring, and he was taking care of a number of patients with Barth syndrome, including Will McCurdy, who you just heard about; and as I took over his clinical practice, the amazing Barth Syndrome Foundation

network recognized there was another doctor getting interested in Barth syndrome, and very quickly I found myself taking care of a third of the U.S. population and recognized that we had to do something about this.

So I and some very special colleagues, who are still working on this disease with me today, got together and started the Barth Syndrome Clinic at the Kennedy Krieger Institute and at Johns Hopkins. This is one of only two multidisciplinary clinics dedicated to Barth syndrome in the world and the only one in the U.S. We established the clinic in 2012, and we're all still together today, 12 years later, holding our clinics. We have a collaborative team in metabolism -- myself -- cardiology, hematology, genetic counseling, physical therapy and nutrition, and we offer quarterly outpatient visits where patients can come and get full assessments. We put together all of their clinical data and we support their local care teams in providing the best care that we can. To date, we've seen over

50 individuals with Barth syndrome, which is about 40 percent of the U.S. affected individuals.

Pretty quickly, after starting the clinic, a lot of really common questions were coming up, and those questions were things from parents like, "How does my child look in comparison to the rest of the population with the kids with Barth syndrome? What does the future look like? What can we expect? How can this disease evolve? How do I know that how I'm treating my child works for them?" I couldn't answer any of those questions, and that really galvanized my team and I to try to identify what we needed to learn and what we needed to know in order to really approach these questions and help our patients.

What was difficult for us, which are really common for a lot of ultra-rare diseases, is there was a lack of prospective natural history studies. There were some very nice small cohorts but nothing that told us what happened in the disease over time. There was a lack of clinical targets for measurements of outcomes, so when patients ask how

do I know if what I'm doing works, it was really hard for us to tell that.

There's a lack of biomarkers correlating to clinical status. As you heard from Reenie McCarthy, the cardiolipin ratio is 100 percent sensitive and specific for Barth syndrome, but we didn't know if that ratio actually correlated to how a patient was doing at that moment, and there's a limited understanding of whether the variants in tafazzin are family specific or no founder mutations and whether those mutations actually relate to a patient's presentation.

So we very quickly, after initiating the clinic in 2012, long before we met Stealth and long before we had a clinical target in mind or product in mind, initiated a natural history study, and with the incredible dedication of the patients and their families, everyone who has attended our clinic has enrolled in our natural history study and we're continuing even now to collect data.

We've had multiple opportunities to actually collect this ongoing natural history, not only in

our clinic but also by attending the biennial Barth Syndrome Foundation international meeting. So every other year, my team and I -- and again, this is the same physical therapist and the same cardiologist who are conducting all of these studies for the past 12 years -- attend all of these meetings as well and conduct studies.

What we've done, we see patients from infancy through adulthood and collect every last possible bit of information we can about these patients to provide the best care we can for our kids, for our patients. This includes cardiology -- you've heard we've set up echocardiogram machines at these meetings -- as well as, of course, in clinic, physical therapy assessments, and the vast array of assessments that Dr. Hornby is conducting for the past 12 years, hematology studies, genetic studies, and we've also been able to collect biological specimens to share with the research and clinical community.

Again, I cannot express my gratitude to the Barth syndrome population and how much they uptook

and how enthusiastic they were about our research. We were able to assess more than 50 percent of all U.S. patients. A number of those patients are babies and children, and every subject that we assessed in the functional studies I'm going to show you demonstrated significant impairment in their function.

So what did we learn? We learned that exercise performance is abnormal in every patient with Barth syndrome. Looking at the panel on the right, this is distance walked on the 6-minute walk test, and what you're actually looking at is standard deviation from normal for what would be expected for both age and for height. You can see that no one performed as expected on the 6-minute walk test.

The 6-minute walk test distance, this is the distance walked on a predefined track with a predefined SOP, every patient received the same exact instructions based on our SOP for how to perform this test. You can also see that not only is everybody impaired, but the 6-minute walk test

gets worse over time in the population. Older individuals had more fatigue, as we did their pre-assessment evaluations, than younger patients, again, consistent with the disease worsening over time. The patients who expressed the most fatigue performed the most poorly on the test, which is to be expected.

What's the next thing we learned? We learned that muscle strength is abnormal in all patients with Barth syndrome. If you look at the panel to the right comparing the dark bars, patients with Barth syndrome, the light bars are controls, there's significant reduction in muscle force generated on hand-held dynamometry in all patients with Barth syndrome, and again, worse with adults consistent with the disease worsening over time.

There were other functional studies we really wanted to include in our evaluations based on what the patients were telling us, so stuff that I think most people take for granted in their day-to-day life, which is like the ease of rising

from a chair, the ease of rising from a toilet in a public restroom. These are things that patients have expressed to us that are very difficult for them, so we wanted to include the 5-times sit-to-stand in our assessments. This is the ability of the amount of time it takes to rise from a seated position without using your hands to push up.

This was significantly, as expected, based on what my patients were telling me, impaired in this population. And one other thing that we wanted to assess, because we know that core strength is really important for balance, is how these patients were performing on balanced testing. Using a SWAY app, which is an accelerometer, we found that patients had significantly impaired balance.

I talked to you about some big cross-sectional studies but cross-sectional studies. What do things look like over time in patients? We actually had the opportunity to look at the same cohort of patients from 2014 to 2016

within the same setting at the Barth Syndrome Foundation meeting, and look and see how those patients performed in that interval time. You can look and see that I don't think we could have been much tighter in the 6-minute walk test that is performed in the 2 years. It's almost identical year to year, showing patients do not improve over time.

If you look at the blue line graph and the green line graph, each point represents the same patient. It's almost like a perfect shift over. Those patients who are much poorer were much poorer, those patients who are much better were much better, with the exception of 2 patients who had major health interval events and performed more poorly due to cardiac situations.

Also, it's really, really important to me that these aren't just numbers; that the numbers we're seeing actually correlate to how a patient's life is, and how they're feeling, and how they're able to get through their day. So we included a lot of quality-of-life assessments, and we found

that across the population, quality of life was severely, severely decreased, as young as children and patients 2 to 4 years of age, and, of course, fatigue correlated to more severe impairments in quality of life. I also might want to add these are things, again, that worsen over time.

You heard a lot so far -- and you will hear a little bit more -- about cardiolipin as a biomarker for disease. Looking at the panels on the right, you can see there have been numerous studies to show -- this is beautiful for a biochemical geneticist -- that the abnormal cardiolipin ratio is 100 percent sensitive and specific for a diagnosis of Barth syndrome, but we didn't know does this correlates to clinical status. So we had the opportunity over these 12 years to actually measure cardiolipin again, and again, and again in patients, and what we found is that the more abnormal the cardiolipin ratio, the poorer a patient performed on the 6-minute walk test. What we also found over time is that cardiolipin ratios, they don't improve, they stay

the same, and if anything, they worsen. So again, you're hearing a theme that quality of life, physical measures, and biomarkers get worse over time.

So I hope I've done my team justice in the work that we've done. I might add this was completely unfunded, done with the enthusiasm of my team really wanting to help our patients and really wanting to understand this disease and provided evidence that functional assessments, including the 6-minute walk test, hand-held dynamometry, 5 times sit-to-stand and balance, worsen over time in our patients. The quality of life worsens over time in our patients and biomarkers don't change or, if anything, worsen over time in our patients. Thank you for giving me the opportunity to speak, and I'm going to introduce Dr. Jim Carr.

Applicant Presentation - Jim Carr

DR. CARR: Good morning. My name is Jim Carr. I'm the Chief Clinical Development Officer at Stealth BioTherapeutics, and I will walk us through the safety and efficacy findings of the

elamipretide program.

Just a little bit of a road map for how the program was conducted, the TAZPOWER trial, as has been talked about, read out in 2018. At the time that that trial read out, there were already 10 patients that were in the open-label extension. So patients were given the opportunity to go into the open-label extension as they were rolling off the double-blind, randomized, placebo-controlled trial. So again, we were already treating patients at the time that the TAZPOWER read out in 2018.

At the time we conducted the TAZPOWER extension trial, we were already starting to think about a natural history control, as has been talked about, and Dr. Joffe set this up very nicely in the beginning. I think there's a recognition of how small this patient population is, so generating additional data, we're dealing with feasibility issues. So again, we were already at that point, thinking about establishing natural history control.

There will be some discussion about expanded

access applications of the drug. I'll talk about safety first, and then I'll talk about the natural history control. I think before we talk about the benefits of the drug, there needs to be an understanding of safety or the risks that might be associated with taking this molecule.

This is from the blinded part of the trial. This is the randomized, placebo-controlled part of the trial. Not surprisingly, there's a lot of incidence of injection site reactions. We're very aware of this. We know why injection site reactions happen. We've actually done a study to identify measures to mitigate this, but most patients that take this peptide will experience some type of an injection site reaction. But aside from the mild to moderate injection site reactions, there are really no off-target toxicities that we've observed. There's really no meaningful separation on other organ systems between drug and placebo.

This was discussed earlier. We have used this peptide in many different disease settings.

This gives us an opportunity to integrate all of those safety findings to give us perhaps a better perspective on any safety risk associated with the molecule. There are over 1700 exposures. There are over 1300 treated patients that are in this database, including over 300 patients with some type of a mitochondrial disease. The profile is no different than what I just described; again, high propensity for injection site reactions, but aside from the ISRs -- and these are subQ or intravenous administrations combined -- in excess of 2 percent, again, ISRs are very common.

There can be some eosinophil rises which tend to be transit and they self-resolve. But again, aside from the injection site reactions, there's no meaningful separation between drug and placebo for the other organ systems. And the same story is true with serious adverse events; again, no meaningful separation on any SAEs have been observed in this program.

At this point, we can transition to a discussion about efficacy. This is the design of

the TAZPOWER trial followed by the TAZPOWER Extension trial. To get into this program, patients had to be at least 12 years of age. They had to be genetically confirmed. Of course, they had to be ambulatory. At that point, they had to meet a weight requirement. The first part of the trial, there was a screening period. They were randomized to drug or placebo at that point. That was a 3-month treatment period.

There was a 1-month washout, then they received the opposite treatment assignment. Ten patients opted to go into the open-label extension; 8 subjects remained on treatment. So when we talked about the natural history control, that would be comprised of 8 treated subjects. The primary endpoints were 6-minute walk test and a patient-reported outcome measurement of fatigue that we developed for this population.

These are the baseline characteristics from the TAZPOWER trial. The average age was 19.5 years of age, and Dr. Vernon talked about this. The mean walk distance, 400 meters for 19-year-old men, I

think most people would agree that's quite diminished.

These are the findings from the randomized, double-blind, placebo-controlled portion of the trial. With a crossover period, one looks at the end of treatment numbers, and it's obvious that there's, one, no meaningful separation, so there's no effect of elamipretide observed over 3 months in the controlled part of the trial, the blinded controlled part. The only endpoint at that point that showed a placebo effect was the 6-minute walk test.

There has been a focus on the period of time from baseline to end of treatment Period 1. It's been talked about that's a 60-meter change, and these are the patients that were randomized to placebo first before getting elamipretide. In fact, what we think happened and what is depicted here in the screening, the screening estimate you can see is about 450 meters. Patients with mitochondrial disease notoriously can really crash after having to perform exercise tests, so we don't

think these patients had fully recovered from the screening performance. So perhaps the baseline was a bit artificially low, but that interval between baseline and end of treatment, that is the 60 meters.

It's important to point out that that end of treatment Period 1, that point estimate is no different than screening, so it's not true that there's effort bias. They don't surpass what they walked originally and, in fact, we don't think these patients physiologically, or biochemically for that matter, can actually perform better at will.

I will also overlay on top of this we were systematically measuring fatigue, and the red line represents a 7-day average of fatigue. So at the the lowest performance at baseline, that represents the highest level of fatigue these patients experienced, which is very common in this disease. If patients are really fatigued, they don't perform as well. Now, as a sensitivity test, and Dr. Wittes will talk about this, we will look at

the value starting from screening and look to see if the effects still hold, and Dr. Wittes will talk about that.

I also need to talk a bit more about, again, this notion of effort dependence, and Dr. Kate is with us, and Dr. Kate has formally studied these patients in exercise physiology studies. With very little exercise provocation, these patients start to retain CO2 and they generate tremendous amounts of lactate.

There's a fair amount of uniformity with these patients. There's some molecular defect. Their ability to have oxidative phosphorylations are greatly diminished, so, again, they generate lactate very quickly. Moreover, they can't train their way out of this, so despite efforts to exercise, train them, they can't perform better. So again, it just calls into question this notion that effort can explain or invalidate the findings from the study.

The conclusions from the first part of the trial, there were no significant findings in the

functional endpoints after 3 months. There was already evidence emerging, however, the effects were being observed, so we continued to treat these patients in the open-label extension, and we quickly turned our attention to attempting to generate an external control. Coincidentally, the guidance industry from FDA had come out at that time, and we tried to follow that guidance to the letter. So we designed the natural history control closely following the guidance to maximize interpretability of the TAZPOWER Extension study data.

Before I start talking about the performance of the endpoints, I'd like to spend a little bit of time talking about the time course of improvement. In many different experiments -- and, in fact, we can show this in humans -- one can detect a bioenergetic effect fairly early; however, it takes days to weeks to restore healthy gene expression, leading to cardiac and mitochondrial protein turnover, and that's true in the Barth syndrome model.

It took us about 24 weeks to start to see improvements in the MLCL to CL ratio, so that took weeks to months. When that happened is when we started to see the biggest benefits on myocardial changes as well as skeletal muscles, and that took months to years. So the expectation is that with this mechanism, it just took longer for the effects to mature.

This is the design of the natural history control study. Again, this is an external control to the ongoing open-label extension. The key inclusion/exclusion criteria are the patients that were getting treated had to have at least 36-week assessments. The natural history control subjects had to be the same age, so they had to at least 12 years of age. That was the the lower limit for the trial. They had to be transplant free. They had to have at least two 6-minute walk test data points to be included in the analysis.

The timepoints of interest were open-label extension timepoint 36, which is week 64, and then week 48, which is week 76. The primary endpoints

were 6-minute walk test at week 64 and then again at week 76. We looked at the secondary endpoints, and Dr. Vernon just walked us through those functional endpoints that existed in the Hopkins' database.

The methods, the naturalist data sources, I think there should be a good understanding of where the data was coming from. It's the Barth Syndrome Foundation International Biennial Conference and from the clinic at Hopkins. Propensity scores, there were multiple models explored using only baseline and selected the model with the best fit. The propensity scores and stabilized weights were utilized to minimize impact of selection bias.

Linear regression is used to estimate value of an endpoint at timepoints of interest. For each subject, a regression line is fitted using all available data, starting with the baseline, and interpolated value was used for comparison between the elamipretide and natural history control groups using a mixed model of repeated measures.

Now, as one can imagine, when we want to

establish a natural history control, it's tempting to just want to look at a database and choose the patients that make your data look the best. That's not how this was conducted. Painstaking efforts were made to create firewalls, so there were protocols, blinding charters, and multiple statistical analysis plans put in place to make sure that this was done in an unbiased manner.

The group, the external group that actually did the matching, only had access to baseline data. We the sponsor never saw the data; we only saw the final report. It wasn't until there was an FDA inspection that we actually saw the raw data. It was requested by the FDA inspector that we produce that, and we never had it, so we certainly never had the data. As I said, the prognostic match team had access only to baseline data.

These are the baseline characteristics of the natural history control compared to the elamipretide-treated subjects. As can be seen, these were highly comparable. When one looks at age, height, 6-minute walk test, muscle strength,

5 times sit-to-stand, and the SWAY balance, again, a fairly equally matched population.

These are the results. I'll walk through this systematically. This is the 6-minute walk test performance. There was a large improvement in the patients treated with elamipretide at most timepoints, so it's about an 80-meter improvement observed at the week 36 or week 64 timepoint and about a 90-meter change. Because there was very little change in the natural history group, these produce highly statistically significant p-values at the end of treatment. I think the magnitude of this difference, again 80-90 meters, I think is inherently clinically meaningful, but these are certainly viewed as clinically meaningful for other diseases.

This is the muscle strength assessed by a hand-held dynamometer. This is lower extremity muscle strength again assessed by a hand-held dynamometer. The same pattern, very large increases in muscle strength were observed with the treated subjects versus very little change in the

natural history control subjects. These were all very impaired at baseline. When one attempts to establish clinical meaningfulness, I think we've heard from the ability to do more and from improvements in quality of life that these are very clinically meaningful. In DMD, these would be considered very clinically meaningful estimates of benefit.

Five times sit-to-stand, as Dr. Vernon talked about, this is a very difficult test for these patients to perform. I think we could have predicted that this might be improved by the increase in lower extremity muscle strength, and that's what was observed. The sample size is a bit smaller in the control group because there weren't quite as much data for this endpoint as well as for SWAY, but the same pattern emerged. A reduction in time is a beneficial change, so it was at least a 2-second improvement at both the week 64 and week 76 timepoint, and similarly, the SWAY balance score, which is an assessment, there's a lot of core strength that is needed to maintain balance.

So I believe this is also a measurement of core strength improvement; again, improvements noted at both timepoints.

This is the multidomain responder index. This is a way to quantify the number of patients that responded. Patients have to achieve at least a 10 percent improvement on these different functional domains. One way to look at this is more patients responded by at least a 10 percent improvement on these endpoints that I just described. The MDRI strongly favored elamipretide at both timepoints, and those p-values were very, very strongly suggestive of a benefit.

Multiple sensitivity analyses performed to pressure test the data. Dr. Wittes will talk about this in more detail but, again, we employed every technique that we could think of to pressure test these findings; and again, Dr. Wittes will talk about this in more detail. All analyses for the 6-minute walk test were confirmatory to p-value of less than 0.001, and similar findings were achieved for all other endpoints, again, when subjected to

sensitivity analyses.

This is a forest plot depiction of the data. This was presented earlier. The key point, the forest plot is looking for concordance of the findings, and as can be observed, all of these horizontal lines are to the right of the vertical line; the farther to the right, the more persuasive the benefit. The right column is the point estimates or the magnitude of the fact. But again, the key point of this type of illustration is the concordance of efficacy, which all strongly favored treatment.

At this point, I will transition to a discussion about the TAZPOWER Extension trial. The natural history part of the trial only went up to the week 72 visit. We did have the opportunity to capture assessments much later, 4 years later. In addition to that, during the open-label extension, I will talk about some findings that were not part of the natural history control.

So at the week 168 visit, and the shaded bar represents the 4-year assessment, for all of these

functional tasks, at the very least, the effect was maintained if not enhanced; again, about 100-meter change in the 6-minute walk test; the hand-held dynamometer again reflected an enduring effect; 5 times sit-to-stand was still exhibiting a favorable response; and then the SWAY balance as well.

The performance of the 6-minute walk test was not at the expense of trying harder, and I will also point out that the assessor was a physical therapist, Dr. Hornby who's the collaborator with Dr. Vernon, so these assessments were not made by the PI; these were done by an independent person. And when the board was used to assess fatigue or shortness of breath, there was no evidence that patients were trying harder to achieve these types of performances.

There are also durable symptom improvements with both the Patient Global Impression of Symptoms as well as the Clinician Global Impression of Severity. In fact, at one point, Dr. Vernon had declared that 5 of these 8 subjects no longer had

symptoms suggestive of Barth syndrome, so a complete amelioration of symptoms. The functional improvements exceed the placebo effect. I will point out that the placebo effect was only observed with the 6-minute walk test. The magnitude of effect was 3-fold that.

Again, we acknowledge it was like the placebo effect on the 6-minute walk test, but the magnitude of effect, which is the way to overcome bias, was again 3-fold higher than that. This was pointed out earlier. There was no placebo effect observed in the other endpoints, so what is depicted here is the placebo effect from the first part of the trial and, again, the corresponding changes that occurred on these different endpoints.

At this point, I will transition to a discussion about the molecular findings, and Dr. Vernon talked in a lot of detail about the cardiolipin ratios. This is a molecular abnormality associated with disease severity. This is the root cause of Barth syndrome. The issue that these patients have is they don't have enough

cardiolipin. They have too much monolyso or immature cardiolipin and not enough cardiolipin. So what was observed was a decrease in this ratio, and we think that's reflective of the fact that cardiolipin's production is either being enhanced or more likely being protected when it was produced.

As Dr. Vernon discussed, no change is expected naturally. This is not expected to change naturally. We saw reductions occur at week 36, 72, and week 168, which were all statistically different from baseline. Interestingly, this week 12 that represents about 6 months of treatment, that corresponds with when these functional improvements were really starting to mature. So we do think that there's a connection between this molecular finding, that is the increase in cardiolipin, and the better performance on functional testing.

I will transition at this point to a discussion about an unexpected finding on cardiac changes. I was starting to detect these earlier

when looking at the baseline characteristics; and these are blinded data, but there was evidence that the end-diastolic volumes were going up. This prompted an interrogation because as members of this committee know, increases in LV volumes can be pathologic.

Barth syndrome is widely characterized as a dilated phenotype, particularly at birth. When babies are born in cardiac distress, they tend to have a dilated ventricle. What we saw was certainly no suggestion of dilation. It was just the opposite. All of the ventricles were small at baseline. This is a Z scoring, so a negative 2 Z score means these are at least 2 standard deviations from what would be described as normal.

The primary feature of the left ventricular volume was that they were small. The ES were all normal. All subjects had a normal ejection fraction. Global longitudinal strain was normal. We systematically follow troponin and NT pro-BNP, and those were normal at baseline as well; but again, the primary feature at this point was small

volumes, and therefore the left ventricular stroke volume was small.

Dr. Braunwald produced a short publication last year talking about mitochondrial cardiomyopathy. This is a classic example of mitochondrial cardiomyopathy. What one might expect in that setting is the non-obstructive hypertrophic phenotype, so perhaps that explains the small ventricles. Barth syndrome is also known to perhaps have an undulating phenotype, so there can be dilation. Maybe this is an intermediate type that we've observed, where basically it's more hypertrophy than dilation, and then dilation can occur late.

Nonetheless -- this is a plotting on the right -- the Medical University of South Carolina was following echocardiograms in these subjects for over 15 years, and one plot, what would be expected for stroke volume over time, there's a a slight decline over time. That, of course, accelerates for patients that experience cardiac death or a need for transplant, but there's certainly no

expectation that stroke volume would improve naturally; and I'm using this as a set-up before I talk about what happened with the trial. What we observed was an increase in left ventricular stroke volume index.

We started to see evidence of this early, so volumes are going up a little bit, and by week 168, that had matured to a stroke volume increase of about 10 milliliters. When one plots that as Z scores, essentially what's being reflected here is, essentially, a normalization of Z scores, going negative 2, getting less negative, which means going back towards normal. This was durable also at week 192. There are 3 subjects at a week 192 visit.

We did have these independently read by an external score lab, and this was corroborated; and again, this is contrary to what one would expect naturally. This improvement in stroke volume -- and these are echo-derived measurements, these are 3D echos -- this was driven by an increase in end-diastolic volume. It was about a

17-mL change in the left ventricular end-diastolic volume index observed at week 168 and, again, we think this is what was driving the increase in left ventricular stroke volume. And again, the Z scores went from a negative 1.6 to a negative 0.46, so essentially a normalization of the Z scores.

This is a plotting of the TAZPOWER Extension based on baseline and, again, what is reflected here is that the Z scores are essentially becoming less negative. The EF never changed, global longitudinal strain never changed. Again, we were following troponin and NT pro-BNP. NT pro-BNP was essentially normal, and it's still normal. There was one patient that experienced excursion up to 53, but aside from that, these patients really didn't experience any excursions in either troponin nor NT pro-BNP.

This is a plotting of all of the data in its entirety. Again, the key point here is concordance with the performance of these endpoints. The farther to the right, the more persuasive the effect. This forest plot pertains to the

open-label extension data, so this pulls in the MLCL and the left ventricular stroke volume, end-diastolic volume, and index data, where again the effect is the same. The concordance of all of these endpoints favor a treatment effect.

In conclusion, the data support a finding of efficacy. There are molecular improvements in the pathognomonic abnormal cardiolipin ratio. By its very nature, we think that's certainly an objective finding. Functional improvements occurred in endurance and strength that were large, clinically meaningful, and durable out to 4 years. Patient and clinician reported improvements in severity of disease symptoms that supported the meaningfulness of these findings.

Cardiac improvements in left ventricular volumes likely contributed to functional recovery. Again, we think by its very nature, knowledge of treatment cannot make the heart work better, so that, too, we think is a very objective finding that benchmarks the endpoints in the middle pertaining to function and feel. In all respects,

these findings go against the well-established and well-understood trajectory of this disease, and at this point, I'd like to invite Dr. Wittes to talk about the statistical methodology from the study.

Applicant Presentation - Janet Wittes

DR. WITTES: Good morning, everybody. I'm Janet Wittes. I'm a statistician. I am a consultant for Stealth BioTherapeutics, but I don't have any vested interest in the outcome of the study. So what I'd like to talk about both to you and to me, somebody who argues strenuously for randomization and who often criticizes historical controls, what is it about these data that have convinced me?

About two years ago, at the Cardiovascular Clinical Trials forum, the CVCT, I was asked to give a short little talk on statistical principles for designing rare cardiac conditions, and at the time, I was thinking of Barth syndrome because we were very involved, and it seemed to me there were really two choices. In an ultra-rare disease, you could do a randomized-controlled trial, which is

what I would have preferred, but the power would be low. In every observation in such a study, you have to look at each observation really carefully before you run blind because everyone is precious, and one little mistake can screw up the whole study.

So that's the randomized trial or you could use a historical control. That would have higher power because you could get more controls but potential bias. And if you used models, you'd have to prespecify the models really carefully so you wouldn't be pulled in by what the data said; and then there were other designs, but those two were the most important. And what was really important, I think, is that when you're using historical controls, or in this case natural history controls, you have to be extremely careful and worried about the potential for bias.

I was amused by by Dr. Joffe's list of strategies to reduce bias today because these are almost the lists that we went through. What is it? Why is this natural history study different from

all other natural history studies? I think there are several reasons. One is, very often in natural history studies, you go and you collect a bunch of data from other studies, and other places, and other times, and then you try to compare them to the active patients that you have, and they're really not the same. Here, the natural history controls and the treated people were almost contemporaneous. The natural history data were collected from 2012 to 2019 and the patients in the study were 2017 to 2019. So these are almost contemporaneous and there was no change in treatment over time.

The other thing that's really remarkable and really important in this case is there was consistency in the data collection team and the methods. It was the same investigator, and you have met her, she's over there, Dr. Vernon, the same investigator for all the patients, the same physiotherapist using the same machines, using the same tests for everybody; a standardized protocol for both the natural history study and the actual

intervention because the natural history study started before there was an intervention, so it's the same protocol used to collect all the assessments. And then every functional test in the natural history data where assessed as endpoints, so it is extremely consistent in data collection and the methods.

Then there were the firewall teams. Dr. Carr described them a little bit. There was a team building the propensity model, and they didn't talk to the rest of us, and they had no access to post-baseline data. So they built a model looking only at the baseline data. And then there was us, the team developing the statistical analysis plan. We didn't talk to the propensity model people and we had no access to the natural history data. And then, of course, Stealth didn't have access to anything. So we try to keep ourselves as separate as possible, again, to minimize bias. And then -- and I'm going to get to this because this is really important -- there were very clear inclusion criteria to reduce the selection bias,

and then lots of kicking the tires at the analysis; "okay, we did some analyses, but what if we did this, what if we did that?" so really aggressive strategies to reduce bias.

So I want to start with the potential for selection bias. What you've seen in your briefing book from the FDA is that there were 79 people in the Barth natural natural history database and 19 controls; and that seems like, well, how can you ever think that these 19, a representative of these 79? But that's not what happened. There are 79 people. Of those people, the question is, how many of them would have been eligible for the treatment? How many would have been eligible for the study? There were only 24. All the rest were ineligible for age, or for where they lived, or for reasons they were not eligible for this study. So the real comparison is 24 to 19, so we're missing 5.

Why were they excluded? They were excluded because there was only one data point. They didn't have a follow-up. Two of them didn't have a

follow-up because they had died, so they weren't doing better than the active people, and the other three, I don't know why they didn't have another point, but had we included them in the analysis, giving them the mean of the active patients, it would hardly have been any difference in the results. So I think that the important thing is the natural history controls, they comprise a high percentage of the patients who could have been used for the comparison. And as you saw from Dr. Carr, the treated and the untreated were very similar at baseline.

Then came the, ok, the kick the tires. How do you look at the analyses? We have these prespecified analyses, and just because something is prespecified doesn't mean it's correct. So you prespecify it, but you have to look at other things. And again, in your briefing book, the FDA points out that propensity models have real problems in small sample size, and I think we all agree with that, so we looked at all kinds of different propensity models, and they all show

basically the same thing.

Then we said, well, what if you looked at each of the functional endpoints in the eight treated patients, you took out the one who did the best so that maybe there were some who did really well, and you took that one out and did the analysis on the other seven, what would happen? Essentially, the same story. What if you looked at other endpoints? So we looked at week 40 and week 52, and those weren't showing very much, as I think you've seen in the briefing book, but week 100 showed consistent results over time.

Then I'm a little embarrassed about this because one makes mistakes when one writes analysis plans. What we had done was in order to make the natural history and the treated as similar as possible, we made regression lines for the two and we interpolated the values for the treatment group from the regression line. And the FDA in the briefing book said, "Well, why didn't you use the actual data? You had the actual data." And I think, "Oh yeah, that's right. We were trying so

hard to make them the same that we didn't use the actual data." If you use the actual data, the actual data are better than the interpolated data so that, in fact, the difference gets bigger and not smaller.

Then the next is the placebo effect. As you've seen from several of the talks before, there is this placebo effect in the 6-minute walk test, not in the other tests, but in the 6-minute walk test, probably explained by fatigue. So what we did was said, "Okay" -- and these last two analyses we did after we saw the the briefing book from the FDA -- "if you take the actual data, not the interpolated data, but the actual observations from the treated patients, and you use the screening test rather than the baseline, what do you see?" And not surprisingly, there's an attenuation of effect because the screening values are higher than the baseline, but both at week 64 and 76, which were the two primary endpoints for the time, and both of them are statistically significant, even in those analyses.

So again, you've seen this slide before, although it's a little bit here separately, so you see 64 and 76 separately from each other. And what you see is consistency of results in terms of benefit of the treatment over the natural history. If you say, "Well, of course these are correlated, and that doesn't tell me very much; just that they have things that are all on the same side, they're correlated." But if you look at the last one, which combines all the measures in a way that accounts for the correlation, then you see a strong effect in both week 64 and 76, very far away from the dotted line of no effect.

So that is why somebody like me, who always wants randomized studies, says that in a case like this, when the study is done in such a careful way and with such attention to bias, and the results are so strong, the results, to me, are convincing. With that, Dr. Chatfield will speak.

Applicant Presentation - Kathryn Chatfield

DR. CHATFIELD: Good morning. My name is Kathryn Chatfield. I'm an Associate Professor of

Pediatrics at the University of Colorado Anschutz Medical Campus and Director of our Cardiac Genetics program. Just a little bit of background on myself, I'm dual trained and boarded in pediatric cardiology and clinical genetics. I started the Cardiovascular Genetics program at our university, and I'm a staff attending on our Advanced Heart Failure and Heart Transplant service. My relevant disclosures are that I have had grant funding from Stealth in the past, and they are compensating my time and travel for being here. I've also had funding from the Barth Syndrome Foundation for some of our research.

I'm going to talk to you a little bit about the Expanded Access Program for elamipretide, and just to remind you that the cardiomyopathy in Barth syndrome, the underlying problem is an energetic defect due to mitochondrial dysfunction that results from this cardiolipin deficiency that we've discussed. It's been described as having an undulating phenotype, and I'm going to explain a little bit more what that means.

It's not uncommon in Barth syndrome for infants -- but really at any age, but in particular infants -- to present with a dilated cardiomyopathy and an end-stage heart failure phenotype. In many cases, this is not recoverable, and that's been discussed; that there's a high morbidity and mortality in infants, but for survivors of Barth syndrome, what we see is there appears to be a compensatory hypertrophic mechanism or hypertrophic response that can lead to a period of stabilization and relative stability over time. But the important thing is that an energetic demand or a metabolic stress can result in a regression to this dilated phenotype and heart failure at any time in life.

In the TAZPOWER and the TAZPOWER Extension studies, obviously the children, and adolescents, and adults are all over 12 years of age, so as a pediatric cardiologist who does advanced heart failure and transplant, I recognize that there's a very high unmet need for some of these children who present in infancy with decompensated heart

failure. I'm going to talk to you about a couple of the cases that we've known about from the Expanded Access Program as examples of this.

The first case was a newborn who presented to Children's National with evidence of decompensated heart failure with lactic acidosis and an ejection fraction at or below 20 percent that was unresponsive to our typical critical care medical therapy. The patient was rapidly and early diagnosed with Barth syndrome, and based on that, elamipretide was requested and was started around 3 weeks of age.

The patient was eventually able to be transitioned on to guideline-directed medical therapy or the conventional oral heart failure regimen that we would try to transition a patient like this to, in addition to elamipretide, and over a period of months, the ejection fraction gradually improved to the low normal range and as high as 55 percent. By 4 months of age, the infant was able to acquire normal developmental milestones, but unfortunately the patient passed away at 5 and

a half months of age. The cause of the death was not known specifically, but on autopsy, it was evident that there was a Klebsiella sepsis.

Another case that I will highlight for you is a case of an 11 month old who was not previously diagnosed who presented to the Children's Hospital of Philadelphia with evidence of decompensated heart failure in the setting of a couple days of a viral illness or a rhinovirus infection. The patient had a low ejection fraction of under 25 percent, and due to his critical nature, within 24 hours of admission, he had to be cannulated on to extracorporeal membrane oxygenation, or ECMO, and over a period of weeks was eventually then transitioned on to a Berlin ventricular assist device for sustained mechanical circulatory support.

The patient was diagnosed with Barth syndrome based on genetic testing, and elamipretide was administered to the patient after these other medical interventions had been implemented on top of the standard of care therapy. And over time, as

observed, the heart function improved substantially, so by 5 months, this patient was able to be transferred across the country to an institution closer to home and, in fact, the VAD was able to be explanted at 7 months after successful wean trial of the VAD.

There are three other cases of infants who, like the first, had presented in the newborn period with symptomatic decompensated heart failure. The first was listed for transplant but initiated on elamipretide and was observed to have improvement both in heart function and other functional developmental parameters. The patient eventually was on oral heart failure therapy and had normal ejection fraction, and we've been told that this patient has now been delisted.

Another patient, likewise, began on elamipretide at about a month of age, and then was able to be discharged after several months of therapy with normal left ventricular size and function. And lastly, one other patient who was admitted in California at 2 months of age was not

thought to be very stable to be bridged to transplant but was initiated on elamipretide and was successfully transplanted at 4 months of age, but the plan had been for this patient to continue the therapy post-transplant.

To provide you with a little bit of context about what these findings mean, again, I would remind you that approximately 15 percent of all patients with Barth syndrome will eventually require a heart transplant, and 30 percent of those patients will require some form of mechanical circulatory support. Most of them end up on ventricular assist devices, but a smaller number also have required ECMO support.

There are no other known cases of myocardial recovery allowing explantation of VAD in a Barth syndrome patient, and when we look at many case reports of successful explants of pediatric patients from VADs, and we know that this occurs rarely, there's one systematic registry-based study from Europe that has shown us that myocardial recovery permitting explantation of VAD can occur

in less than 10 percent of patients. It has also been shown in that study that the majority of those patients were not genetic cardiomyopathy patients, but the majority of them were patients that suffered from myocarditis.

Thank you for allowing me to speak, and I'll pass back to Reenie for some concluding remarks.

Applicant Presentation - Reenie McCarthy

MS. McCARTHY: I will be super short because I know we need to get to questions. I only have a couple of slides, and I will blow through them.

In conclusion, we believe that elamipretide for the treatment of Barth syndrome supports a favorable benefit-risk determination. Safety I think is uncontested in terms of no material safety concerns being identified and consistent approval of expanded access for the most vulnerable of patients. We've seen efficacy results in the cellular signature of this disease, the cardiolipin ratios in how patients are functioning, in how patients are feeling, and in how their hearts are functioning. These have been durable over a 4-year

period, and they are completely unexpected in the natural course of this disease. I won't cover the regulatory standards again.

Dr. Wittes spoke very eloquently about the statistical concerns here, which we recognize are incredibly relevant in the setting of a natural history control trial, but we do feel that we've addressed the FDA's concerns with selection bias; placebo response on the 6-minute walk test, the only endpoint on which that was observed; and the propensity score model development process and imputation. We can come back to this side but, again, I want to allow the committee to get to questions.

In terms of the questions that have been put for you for consideration, just a note that in the TAZPOWER Extension study, durable improvements out to week 168, which is about 4 years of therapy on the 6-minute walk test, which was improved from both screening and baseline; muscle strength; 5 times sit-to-stand; balance; heart function; and patient reported outcomes. Similarly in the

natural history control study, these improvements were completely unexpected in the natural history. These findings are consistent with our findings in our patients with primary mitochondrial myopathy due to nuclear DNA mutations, where we are in phase 3 development with FDA's blessing and across multiple nonclinical models.

In summary, the totality of the evidence -- and you've seen these slides -- favors treatment, and the need for an approved therapy is urgent now. Children and young men are leading lives that are significantly limited by this devastating disease. There aren't any therapies approved. There's nothing close to clinical development. And I can personally attest, after 10 years of trying to develop a drug for this disease, that even if there were other therapies in the pipeline, it would take many, many years to recruit and conduct additional studies, even if powering considerations were considered feasible in that setting.

We've committed to further research through

a proposed postmarketing disease monitoring program. We are asking you to conclude, based on the totality of the evidence we've shared, that the benefit of elamipretide outweighs the risks, supporting the approval of elamipretide for Barth syndrome. And with that, thank you for the extra time, and I'd be happy to take questions.

Clarifying Questions to the Applicant

DR. BUTLER: Thank you very much.

We will now take clarifying questions for Stealth BioTherapeutics. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up questions with, "That is all for my questions," so that we can move on to the next panel member.

Again, just as a reminder, please raise your hand. Commander Bonner and myself will keep tabs

so that we can go in line, and for any follow-up questions, just raise the thing. Our colleagues who are online, please raise your hand online, and we will follow with that as well.

Are there any clarifying questions for the presenters?

Dr. Ellenberg?

DR. ELLENBERG: I have two questions. First, I'd like to understand, with regard to the natural history study, it sounds like some of these patients were included during the same time frame as the interventional study was conducted, so I would like to know why -- they were eligible for the study -- they weren't in the study; and then my other question relates to a particular slide.

MS. McCARTHY: Dr. Vernon, I'd love to invite you up to answer that question, please.

DR. VERNON: I have a couple of answers for you for that. The first thing is, we enrolled incredibly quickly, so we were fully enrolled within 3 months, which is kind of amazing if you've done these kinds of clinical trials; and a lot of

this is because of the uptake from the population. So we enrolled really fast, so we met our 12 pretty quickly.

The other thing that limited some patients coming to us to participate in the study was there was actually a physical therapy study that was looking at exercise outcomes in some patients, and based on our inclusion/exclusion criteria, that was actually considered to be an interventional study. So patients who participated in that exercise study couldn't enroll with us. There was technically sort of a competition for enrolling that excluded some of those patients. I think that probably covers most of those concerns.

DR. ELLENBERG: Okay. There were 12 people entered into the interventional study, but we saw data on 8 of them. What happened to the other four?

MS. McCARTHY: Thank you for the question. I'll try to answer it, and I'll call up help if I need to. As Dr. Carr mentioned, all patients were eligible to go into open-label extension, but only

10 elected to go into open-label extension. We don't have that long-term data, although we did do sensitivity analyses, including all 12, in the natural history control studies, so we covered that in sensitivity analyses. Two didn't go into open-label extension, and ten did. Of the ten, two withdrew early from open-label extension due to injection site reactions. Both have requested to come back on to therapy.

DR. ELLENBERG: I'm sorry. The two who didn't choose to go into the extension, why did they choose not to do that?

MS. McCARTHY: Oh, gosh. I think one, it was college and not wanting to come for frequent -- I mean, this is reported to me -- visits, and the other didn't like injecting himself daily.

DR. ELLENBERG: I do have other questions, but we don't have so much time.

DR. BUTLER: Okay.

Dr. Gerhard online?

DR. GERHARD: Hello. Tobias Gerhard. This

really follows up the last part of the previous question. Do we have the data for the two people that didn't participate in the extension study, and also do we have the data for the two people that dropped out early during follow-up in the extension study? Both of these -- so four total -- about a third of the total treated population in SPIBA-01, did not participate. So if we could look at their performance while they were observed compared to the patients during the same time periods that went on to be in SPIBA-001, that would shed some light on the potential for selection bias from not including that one-third of the originally randomized treatment population.

MS. McCARTHY: We did do sensitivity analyses to include these patients in the SPIBA-001 analysis and did not see a change, but in terms of their actual data, let me see if we can come back to you after the break. We just don't have slides prepared for that. We can see if we can come back to you with some more responsive information there.

DR. GERHARD: Thank you.

DR. BUTLER: Just a reminder to the panel members, please state your name for the record.

Dr. Shaw?

DR. SHAW: Thank you. Pamela Shaw. I just had a couple of quick clarifying questions about the natural history study and the method of analysis. My understanding is you were looking at these primary endpoints. I think it was 68 weeks and 72 weeks.

The first question, you used an imputation technique, and I wanted to clarify that was a single imputation technique where you drew a line, you interpolated, and then you treated that as an observed point. So you didn't use a multiple imputation technique, but a single imputation.

MS. McCARTHY: Dr. Wittes?

DR. SHAW: Yes, that's the best person. Thank you.

MS. McCARTHY: Certainly better than me.

DR. SHAW: Yes.

DR. WITTES: Yes, that's correct. For the natural history, we simply took a line and then

interpolated those two. For the treated, as I said, in response to the FDA briefing book, we actually did use the actual data.

DR. SHAW: Okay. The other two quick clarifying questions related to that, what was the average distance and time between the observed data in the natural history and those interpolated points? If you have any pictures of those data, it would be interesting to see the distance.

DR. WITTES: Yes. I don't know whether we have -- we've certainly prepared them. We have spaghetti plots of all those data. I will say they were variable, and I guess if we don't have it here, we'll try to get back to you later.

DR. SHAW: Yes, that's fine. I guess the final point there, it sounds like in the analysis, when you use an outcome that is predicted in place of an observed, there are two statistical issues that arise and this post-prediction inference. The first is there's actually bias in association parameters because it's just not a valid inference technique to use a Y-hat instead of a Y, a

predicted value, because it doesn't have the right distribution, so you mess up association parameters.

The second thing is that any kind of p-value that doesn't take into account the uncertainty of those imputations is no longer relevant to the actual uncertainty in the data. It's only relevant to the imputed values, which aren't actually the data. And just to be clear, you didn't take any statistical adjustments for those two problems that can occur statistically when you use an imputed value in place of a data point, mainly the biased p-values and the biased association parameter.

DR. WITTES: Well, I think afterwards, using the actual data, I think that avoids the problem that you're addressing. That's the first issue.

Can you describe the second one again?

DR. SHAW: Yes. You made no adjustment to the p-values for the uncertainty in the imputed values.

DR. WITTES: Well, yes, that's correct.

DR. SHAW: Okay. Thank you.

MS. McCARTHY: Just as a quick follow-up, there were observed values for, I think, 15 or 16 of the natural history control patients at week 100 because that would have spanned the time frame of collection for those. When we did the two observed values analyses, that also demonstrated benefit.

DR. BUTLER: Thank you.

Dr. Kishnani?

DR. KISHNANI: Yes. This is Priya Kishnani, and I had a couple of questions. One was the time of the day and the order of testing for the 6-minute walk distance, because that really plays a very important role in a condition where there is so much fatigue. The second question, which maybe I should ask at the same time, is in slide number 88, -- and I'm not a statistician, so that's my disclosure. It says that there was a jackknife approach that was taken, and this was more related to the treated patients, taking out the outliers and the best responders.

Was that same consideration given to the natural history cohort? So the patients who were

doing the least well, were they also excluded to remove any kind of bias?

MS. McCARTHY: I'd like Dr. Vernon to speak to the 6-minute walk test in the order of testing, and we will then come back with an answer on the second question.

DR. VERNON: For the SPIBA-201 studies, for the clinical trial, all of the studies were done in the same order at the same time of day for every patient, for every observation.

MS. McCARTHY: And I'll ask my colleague, Anthony Abbruscato, to speak to the second question regarding the natural history control cohort.

DR. ABBRUSCATO: Hi. I'm Anthony Abbruscato from the clinical team at Stealth BioTherapeutics. The question was whether the jackknife resampling was performed on the natural history cohort. This was only applied to the treatment cohort, so we removed the greatest responder from the treatment cohort. I will say that for the natural history cohort, the average trend was pretty flat, so the data were pretty tight there, but we did not remove

the patient who performed the worst on that assessment. Thank you.

DR. BUTLER: Dr. Jonsson-Funk?

DR. JONSSON-FUNK: Yes. Michele Jonsson-Funk, University of North Carolina. My question has to do with the data that are being collected through the biennial conference that you hold. I'm curious to know what, if any, information you have that might inform whether individuals who attended that session, at which these repeated measures could be collected, were generally healthier due to the need to travel to attend that meeting or unhealthier motivated by coming to get more information about potential new treatments, for instance.

MS. McCARTHY: Yes. I'll try to answer that question but certainly can ask Dr. Vernon or Kate McCurdy to add in if I don't adequately do so. Remember that for Johns Hopkins as well, patients are traveling from all over the country, as well as internationally, and these are well-visit clinics that are being held, so I don't think that there is

an expectation that patients are different between the two groups. But, Dr. Vernon, maybe you can add your perspective.

DR. VERNON: I think that given the fact that the 6-minute walk test is consistent across all of the studies that we've conducted, those at clinic and those done at the meetings, as well as those done at baseline for the study, are pretty much the same. I don't think that there's any difference. In thinking about the patients who both travel to the clinic and travel to the meeting, they really all seem quite consistent to me. I don't really exactly have the numbers in front of me, but everybody seems to be about the same.

DR. JONSSON-FUNK: Thank you.

DR. BUTLER: Dr. Kishnani, your virtual hand is still up. Do you have a follow-up question?

DR. KISHNANI: Yes. Was that for me? I do have a follow-up question, and this is with regards to the safety. Somewhere in the slide -- I don't recall the number -- there was mention of a medical

device that was stated. I don't quite understand if this is a subQ injection, what the role of the device is. Second, the injection site reactions, it appears what was noted was erythema, but did any of them progress to lipoatrophy, or hypertrophy, or anything else?

MS. McCARTHY: I'm going to ask my colleague, Jim Carr, to speak to that question. I will say, while Jim approaches the podium, that the medical device was a multi-use pen injector that was utilized in some of our other interventional trials in patients with dry age-related macular degeneration. In primary mitochondrial myopathy, it was actually harder for the patients to use. With mitochondrial dysfunction, our CNR muscle group is actually pretty compromised, so we abandoned utilization of that device. It wasn't used in the Barth syndrome setting again.

DR. CARR: Again, Jim Carr, the Chief Clinical Development Officer. Regarding the question about whether the injection site reactions led to, I think, skin disorders, there have been

some occasions. It's infrequent. Reenie mentioned the use of the device. It was actually a single-use device applied to the skin. That actually led to some adverse reactions in and of itself, so these were device-related AEs. There have been some skin condition breakdown essentially from that device. In duration, for example, there can be some lasting site irritation.

As I mentioned before, we've learned a lot about how to manage this. There's a receptor on mast cells that's activated by cationic peptide, so we know why they happen. I think our mitigation approaches, we're intervening early enough so that we don't see any long term sequelae in most subjects that experience injection site reactions.

DR. BUTLER: Dr. Alexander?

DR. ALEXANDER: Caleb Alexander. I have two questions. The first is about the results of the trial and trying to reconcile that with the results comparing the extension study with a historical cohort. And the question is, given your confidence that this product works, what accounts for the

negative findings in the randomized trial and other phase 2 and 3 studies of other mitochondrial disorders or cardiomyopathies? In other words, why is the only affirmative evidence, that might plausibly be considered adequate and well controlled, from a single-arm trial with an external control?

MS. McCARTHY: Yes. In the setting of the TAZPOWER trial, as we said, we don't think that we treated long enough. I think when you look to the movement, for example, of the molecular biomarker of cardiolipin, which started to happen at 24 weeks of total exposure, commensurate with some of the functional improvements, that underpins that learning we had that we needed to treat for longer. I would say, similarly, some of the other trials you're referencing in heart failure were 1-month studies and really designed as phase 2As to inform future development. Signals were observed, but they were underpowered and short. So again, those were more for learning, but that's part of the issue.

We did do a fairly large development effort in primary mitochondrial myopathy, and in that we enrolled patients with a large heterogeneous basket of mitochondrial and nuclear DNA mutations, which was part of FDA's guidance, really, to study rare diseases to try to treat more patients. We had prespecified in consultation with the agency because we were concerned about that variability, and what we saw in patients with mitochondrial DNA mutations, which due to a concept called heteroplasmy can actually differentially affect different cells in our body, there was a large placebo effect in patients with very low levels of mutation load.

However, in the nuclear DNA patients that was an N of 59, in that trial we saw a statistically significant improvement on the 6-minute walk test at 6 months. And with that, FDA has agreed that that data is supportive of registration, and we are doing the confirmatory study now, which is a fully enrolled 100-plus patient phase 3 trial in patients with nuclear DNA

mutations. I would point out that Barth syndrome is a nuclear DNA disease as well. We're also in phase 3 in dry age-related macular degeneration based on a significant improvement in photoreceptor protection in that disease.

DR. ALEXANDER: Thank you. So the mitochondrial trials that are underway are much longer duration, then?

MS. McCARTHY: They are now. Barth syndrome largely informed that. The trial that we did in mitochondrial myopathy was a 6-month study. Again, in the patients with nuclear DNA mutations with a more homogeneous mutation load, we saw significant improvement on the 6-minute walk at 6 months versus the 3 months that we studied in Barth syndrome, but our ongoing phase 3 is now for a year.

DR. ALEXANDER: Thank you.

The second question has to do with external controls. You can't match your way out of the concern when you're using a historical control with an effort-dependent outcome. You've provided lots of very good best practice approaches to try to

minimize the validity threats posed by historical control, but no amount of matching can overcome that potential concern, so my question is about the randomized withdrawal study.

When I read the FDA's briefing and listen to your comments, I hear a variety of different reasons why it wasn't undertaken, so I just wondered if you could clarify. The FDA noted that the applicant was uncertain when symptoms would recur, and that was the basis for your lack of enthusiasm for that approach. What I heard you say was that the FDA didn't indicate that they would accept this study design; and then I also heard you say that such an approach would be underpowered.

So it would be helpful to hear more from you about whether or not -- if you could just address those various points and just clarify why a randomized withdrawal study was not performed.

MS. McCARTHY: Sure. I'd be happy to. Keep in mind this has been a long development effort with four different review divisions of the FDA involved and a disease in a very small indication

that was challenging for both us and FDA. When the randomized withdrawal protocol was proposed in 2019 by the Division of Neurology Products, we raised the concern that it could be underpowered with only 8 patients left in open-label extension to show benefit, and we were told by DNP that something directional on a patient-reported outcome might be appropriate. The program was then transferred through a couple of different review divisions. There was some repeated reference to that trial.

So in 2021, we proposed two different randomized withdrawal protocols utilizing the natural history control subjects, all eight still on therapy, to the Division of Cardiology, and we were told that due to the underpowered nature of that trial, it would be within the division's purview to put the trial on clinical hold. We could proceed with it, but it would not add any evidence of efficacy to support our application. So, as you can imagine, we didn't want to proceed with putting patients through that withdrawal given we were told that it would no add no evidence.

There were other randomized-controlled trial protocols that were proposed by us during the ensuing period. In each case, powering concerns were raised as really giving significant pause to the agency, and we would have wanted alignment to undertake an effort that massive in a disease this rare.

DR. ALEXANDER: Thank you.

DR. BUTLER: Dr. Peterson?

DR. PETERSON: Yes. Eric Peterson. Just a couple questions, first for Dr. Vernon, who I think would be best to answer this. It revolves around that correlation between changes in your cardiolipin ratio or the biochemical marker of success and changes in symptoms. You should have data both in natural history patients who are not treated. Is there a correlation between a worsening or an improvement in that cardiolipin ratio and symptom change? Then similarly, do we have that same change data -- you should also have that from the patients who were treated.

Do we see the patients who were treated --

DR. VERNON: No, no, no.

DR. PETERSON: -- sorry.

MS. McCARTHY: I'm just synthesizing to make sure that I answer your question properly. I want to be very careful that I'm not talking about statistical correlation because that is very much outside of my area. So what I can say is that, statistically, the patients whose cardiolipin ratios were improved were better than other patients and had better 6-minute walk distance. And patients who have better 6-minute walk distance have better quality of life, but I don't think statistically I can make that connection and be proper about it.

Does that make sense? Did that answer your question, I hope?

DR. PETERSON: Yes. Did you see that in both groups, the natural history study, as well as in the --

DR. VERNON: In the SPIBA-201? Oh, yes, for sure, certainly. As the patients' functional measures improved and their cardiolipin measures

improved, their quality-of-life outcome on PROs also improved, yes.

DR. PETERSON: A follow-up question then; do you have a sense that of all the patients who are treated, what percent do we see that improvement in -- you gave average results on everything. There could be a potential non-responder of a section of patients. Do you have any idea what percent of patients are responsible for that or is it an average across all the patients?

DR. VERNON: I'm not sure. I'm sure that Stealth --

MS. McCARTHY: Slide up. This is showing you all the cardiolipin ratio data. This is really a spaghetti plot sharing every patient on long-term elamipretide with cardiolipin ratio data. We do have a slide, which we can come back to you if it's not pulling up right now, that, really, if you overlay the 6-minute walk distance on a spaghetti plot for these patients, you see the improvements, really, at the same point in time for 6-minute walk test differences. Again, we'll pull that up for

you in just a moment.

DR. PETERSON: And you're just anticipating, then, that the change in cardiolipin ratio, which looks like it improves as early as 12 weeks --

MS. McCARTHY: Twenty-four weeks of total exposure, but yes.

DR. PETERSON: Right.

MS. McCARTHY: Yes. That's when we saw improvements in 6-minute walk.

DR. PETERSON: That's symptomatic improvement --

MS. McCARTHY: At the same timepoint for the same patients. You can actually almost overlay it when you're looking at the 6-minute walk test differences. Again, we'll get you that slide; I promise.

DR. PETERSON: That would be great.

Then one second question, and I think Dr. Wittes may be most appropriate to answer this. When the presentations of the LV function change were given, the answer was that that was an unexpected finding, which then made me wonder how

much of this was prespecified versus was this not prespecified; first question. Then, were there a lot of other specified outcomes that we're just not seeing? We're seeing a selection of those that are positive.

MS. McCARTHY: I'll actually asked Dr. Carr to take that question. Cardiac echocardiograms were being followed primarily for safety, so they were all prespecified, but Jim can speak to the emergence of the signal we saw.

DR. CARR: So we certainly didn't prespecify any particular echo parameter that was being followed. As FDA has pointed out, there were many different echo parameters being followed, but we didn't prespecify; for example, left ventricular and diastolic volume index. Again, basically, the echo parameters were being followed in their entirety.

DR. PETERSON: Then how many prespecified endpoints did you have, in total in the SAP?

MS. McCARTHY: There were two other PROs. There was the PROMIS Fatigue -- the prespecified

endpoints were the 6-minute walk test; the Barth syndrome symptom assessment of fatigue. This is in the TAZPOWER crossover trial, so all of those then we follow in open label. So those were the two primaries, 6-minute walk and fatigue with a PRO that we developed specific for this patient population.

The secondaries prespecified were 5 times sit-to-stand, muscle strength measured by hand-held dynamometry, SWAY balance. There was a PROMIS Fatigue scale as well. There were some other domains on the Barth Syndrome Symptom Assessment, and there was the Patient Global Impression of Symptoms and the Clinician Global Impression of Disease Severity. So we've shown you all of those, I think, other than the PROMIS Fatigue, which looks very similar to the Barth Syndrome Fatigue Assessment.

DR. PETERSON: Thank you.

DR. BUTLER: Ms. Shuman?

MS. SHUMAN: Hi. This is Devin Shuman speaking. I had just one really quick question,

and then two that I'm not sure if you have the data available or not. The quick question was slide 55 where you're talking about the effort bias. You did discuss the time frame between screening and the baseline assessment, but I don't think I saw on any of the slides what was that actual time frame, from the screening data, the baseline.

MS. McCARTHY: It was between 2 and 4 weeks for these patients. So there was a range, so it was between 2 and 4 weeks.

MS. SHUMAN: Then follow-ups to two other things people brought up, really quickly. One, you did mention that some people were not included in the natural history control, in part, because they were participating in that physical therapy study beforehand, or they weren't in the initial one but they were in natural history. Do we know how many people participated in the PT study, and then also participated in the natural history cohort?

MS. McCARTHY: I'll have Todd Cade come up to answer that part of the question on the exercise trial, which may be of independent interest. I

don't know that we've mapped the overlap between that and the natural history cohort.

DR. CADE: Good morning, everyone. My name is Todd Cade. I'm a physical therapist and a clinical researcher, and the Division Chief and Professor at Duke University School of Medicine. I apologize for my voice. I'm losing my voice. My relevance to this meeting is we've been doing metabolism and exercise studies in humans with Barth syndrome since 2008. I would like to disclose that I am a member of the Scientific Advisory Board for the Barth Syndrome Foundation, and I'm serving as a consultant for this meeting that we're at today.

So the question is, some of the participants were participating in an exercise program, and that was my study. So we did an exercise program using resistance training. It was a 3-month program, and there are 5 subjects that participated in it. I don't know about the overlap, but I think that some participants were not able to participate in the elamipretide trial because they're in my trial.

MS. SHUMAN: Okay. Then a last quick question that, again, we might not have the info for. But I know that in some of the letters that people wrote in, there was at least one participant, and he said that he was a part of the Stealth trial and was first in the initial phase, is what he talked about being on the drug. He was taken off, and then later he participated in the OLE but then was taken off again due to a reaction.

Do we know if there was a group of patients that were in and out of getting a treatment during this process whose data might have been included?

MS. McCARTHY: No. All 12 patients who enrolled in the TAZPOWER double-blind, placebo-controlled crossover trial completed therapy. What you would be likely referring to is the patient reporting a washout period in between the two treatment periods, between which they were randomized to either elamipretide or placebo. Then, as we mentioned, two of the 10 patients who enrolled in open-label extension did withdraw, one around 24 weeks and one around 36 weeks, due to

injection site reactions. But all 12 subjects completed the TAZPOWER crossover trial, and indeed that completion was a prerequisite to participation in the open-label extension.

If we have the spaghetti plot of the 6-minute walk, it would be great to pull that up, please; the spaghetti plot, not that, from -- never mind. We'll get there, if there are other questions.

MS. SHUMAN: No. That's the end of it. I will note that I found it interesting that that participant stated that he would have liked to stay on the drug, but he wasn't given that option based on his reaction. So I think that's telling, but thank you. That's all.

MS. McCARTHY: Thank you.

DR. BUTLER: Dr. Berry?

DR. BERRY: Berry, Boston. I have two questions. One is some clarification on noncompaction. Is this a phenomenon that exists in the majority of patients; and if not, does it play any role in whether you have a beneficial effect or

not?

MS. McCARTHY: Dr. Towbin, who is actually the grandfather, or godfather, of Barth syndrome cardiomyopathy, is on the phone, so I'd like Dr. Towbin to take that question, please.

DR. TOWBIN: Hi. Thanks for the question. I'm Jeff Towbin, and I'm the Executive Director of the Heart Institute and Chief of Pediatric Cardiology at Le Bonheur Children's Hospital in Memphis. I'm also a cardiac geneticist.

Non-compaction, which is one of my favorite disorders to follow, does have an impact with this patient population, particularly when it's an overlapping phenotype, and that's the usual scenario. You have hypertrophic dilated cardiomyopathy with noncompaction. If you compare that group versus just the straightforward hypertrophic or dilated cardiomyopathy, you have the worst outcome with the overlapping phenotype group. But also age of presentation is very different between presentation of the babies, which if they don't get transplanted, they all die, so

they don't get to be the 28 year old that you heard of earlier. So there are no good therapies for those, and standard dilated or hypertrophic therapies alone don't change that.

You've heard about the VADs making a difference in that patient population. That is a little bit of a game changer, but still the outcomes in that patient population without transplantation is generally a death outcome. I hope that answers your question.

DR. BERRY: I see. Thank you.

And the other question, if it's appropriate at this time, it concerns their diet. In the individuals who are --

DR. BUTLER: Dr. Berry, can you speak in the mic, please?

DR. BERRY: Oh, yes. Sorry.

Are the majority of the patients who were in the long study, did they have a G-tube? The majority of the patients, did some of them actually require having a port in for diet? I'm curious as to whether problems with dietary intake or total

calories are influencing whether they might have a beneficial effect or not from the point of view of nutrition.

MS. McCARTHY: I'd like Dr. Vernon to speak to the presence of a G-tube for these patients in the trial. What I can tell you is that we -- and Kate McCurdy can speak to this as well -- did document case study notes of Dr. Vernon's during the trial, as well as in the patient perception of change videos. The patients' appetite and ability to eat was improved on elamipretide therapy.

Dr. Vernon, can you speak to how many had G-tubes?

DR. VERNON: I'm doing my best to count in my head. I can say that everybody, with the exception of -- so 11 out of 12 -- I think I'm right -- had a G-tube at some point in their life or during the study, which is really representative of the entire Barth syndrome population that I take care of. I made an effort, actually, not to change anybody or make extra dietary recommendations because as chemical geneticists, we consider that a

form of treatment, so I didn't want to add additional treatment on to what we were already doing at baseline. So I tried not to touch any of that, but very representative of the entire population.

DR. BERRY: The only reason I brought it up was because of the possibility that if the total calorie intake wasn't as good, you might not see the beneficial effect.

DR. VERNON: Oh, for sure. That is a frequent conversation we have, is that you can't make muscle unless you take in protein, but I tried not to make that a medical intervention, but more of my ongoing conversation with my patients.

DR. BERRY: Thank you.

DR. VERNON: Sure.

MS. McCARTHY: If you can bring up --

DR. BUTLER: Thank you very much.

MS. McCARTHY: -- the 6-minute walk slide for a second. I'm sorry. Can I put up the slide for Dr. Peterson? Slide up.

You can see the spaghetti plots of the data

on 6-minute walk versus the cardiolipin ratios. Remember, cardiolipin ratio we want to see go down; 6-minute walk test we want to see go up. There's obviously some variability from visit to visit in the 6-minute walk test, but overall, all of the patients were improving within that same time period that we started to see the significant improvements in cardiolipin ratios.

Does that help?

(No audible response.)

MS. McCARTHY: Okay. Thank you. Thank you for the patience on that.

DR. BUTLER: Well, thank you very much. These questions are incredibly important for the subsequent deliberations of the committee, but we are running late as well. So what I suggest is that we at this point take a quick 11-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourself or with any member of the audience. If the Stealth team can pull some of the data that the panel members have requested, and

if the panel members can jot down their questions, there is more time for clarifications after the lunch break as well. So we will take it up at that time, and we will reconvene at 11:00.

(Whereupon, at 10:49 a.m., a recess was taken, and meeting resumed at 11:00 a.m.)

DR. BUTLER: Well, welcome back. We will restart the proceedings, and we will now proceed with the FDA's presentation with Dr. Ann Punnoose.

FDA Presentation - Ann Punnoose

DR. PUNNOOSE: Good morning. I'm Ann Punnoose, a clinical reviewer in the Division of Cardiology and Nephrology. We will be discussing data submitted to support the efficacy of elamipretide. This is a joint clinical and statistical presentation.

As previously mentioned, the applicant is seeking approval of a new molecular entity, elamipretide, for the treatment of patients 12 years or older with Barth syndrome, and the FDA is soliciting advice from the advisory committee on whether elamipretide is effective for the proposed

indication based on the available evidence.

First, I will briefly summarize the regulatory standard for effectiveness. You heard more about this topic in Dr. Joffe's opening remarks. As discussed in the draft guidances on substantial evidence of effectiveness, published in 2019 and 2023, a drug's effectiveness must be established prior to approval, based on substantial evidence. Substantial evidence generally requires at least two adequate and well-controlled clinical trials, each convincing on its own. When more than one adequate and well-controlled investigation is neither feasible nor practical, FDA may consider convincing evidence from one adequate and well-controlled clinical investigation, together with confirmatory evidence as substantial evidence.

To establish effectiveness, it is essential to distinguish the effect of drug from other influences such as spontaneous changes in the disease, placebo effects, or biased observations. This is accomplished by the features of an adequate and well-controlled clinical investigation.

Dr. Joffe covered several features in his opening remarks. I will show some of them again on this slide.

One feature is a study design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. Another feature is adequate measures to minimize bias and assure comparability of the study groups. A third feature is well-defined and reliable methods of assessing subjects' response; and lastly, analysis of study results adequate to assess the effects of the drug.

In this presentation we will be discussing the clinical studies that the applicant conducted to assess elamipretide's efficacy. These studies are SPIBA-201, Part 1, a randomized, double-blind, placebo-controlled trial; SPIBA-201, Part 2, a single-arm, open-label extension study; and SPIBA-001, an externally controlled study. The applicant also cites other information as confirmatory evidence such as nonclinical findings, biomarkers, and patient/caregiver perception of

change assessments. In this presentation, the FDA will provide our assessments of these studies and data.

First, I will present an overview of Barth syndrome. As the applicant presented, Barth syndrome is a rare, serious, life-threatening disease. It is an X-linked recessive mitochondrial disorder. It is caused by defects in the tafazzin gene that result in cardiolipin abnormalities, leading to mitochondrial dysfunction. There is a worldwide incidence of 1 in 300,000 to 1 in 400,000 live births. It is diagnosed by genetic testing or by an elevated cardiolipin ratio.

Barth syndrome is an infantile onset cardioskeletal disease characterized by cardiomyopathy; hypotonia; growth delay; neutropenia; fatigue; and exercise intolerance. The mortality is highest in the first 4 years of life, with cardiomyopathy being the leading cause of death. Survivors experience improvement or stabilization of their cardiac function in the middle childhood years. The predominant

manifestations in adolescents and young adults are fatigue, poor stamina, and exercise intolerance. Currently, there is no approved treatment for Barth syndrome. This disease represents a significant unmet need.

Now, we will talk about the data the applicant submitted to support the effectiveness of elamipretide for treatment of patients with Barth syndrome. The applicant proposes that elamipretide penetrates the cell membranes and transiently localizes to the inner mitochondrial membrane, and that it ameliorates the cardiolipin deficit and the associated electron transport chain deficiencies, improving ATP synthesis in dysfunctional mitochondria, improving mitochondrial morphology, and preventing the pathological formation of reactive oxygen species. The applicant states these effects improve cellular bioenergetics and reduce pathological apoptosis or necrosis.

The FDA review of nonclinical data for elamipretide supports the proposed mechanism of action relating to improvement of mitochondrial

function. Elamipretide localizes to and is enriched in the inner mitochondrial membrane, the hypothesized sites of therapeutic action, and it improves mitochondrial morphology and function in Barth and non-Barth models. However, it is uncertain whether elamipretide reduces apoptosis and necrosis and improves cardiac structure and function in Barth syndrome models.

This table summarizes the observed effect of elamipretide on certain parameters in Barth and non-Barth models. Elamipretide improved mitochondrial structure and function in both models. There are no data submitted on the effect of elamipretide on apoptosis and necrosis in Barth models. There was no improvement observed in cardiac function or cardiolipin ratio with elamipretide in Barth models.

Of note, there are numerous published trials of elamipretide in other conditions such as other mitochondrial diseases, heart failure, et cetera. Some early stage trials reported improvements, but these were not confirmed in subsequent trials. For

example, a small phase 1-2 trial in patients with primary mitochondrial myopathy showed a significant increase in 6-minute walk distance compared to placebo, but a subsequent larger 24-week, phase 3 trial did not confirm these changes. A small cardiomyopathy trial showed some changes in echocardiographic parameters after a high-dose infusion, but a subsequent larger phase 2 trial did not confirm these changes.

Now, I will be discussing SPIBA-201, Part 1 or TAZPOWER. SPIBA-201, Part 1 was a phase 2, randomized, double-blind, placebo-controlled crossover trial to evaluate the safety, tolerability, and efficacy of elamipretide in subjects with genetically confirmed Barth syndrome. This schematic shows the design of SPIBA-201, Part 1. There were two periods within Part 1. Each period was 12 weeks long and separated by a 4-week washout in between. Subjects in Part 1 were either on Sequence EP or Sequence PE. Subjects in Sequence EP received elamipretide in Period 1, followed by placebo in Period 2. Subjects in

Sequence PE received placebo in Period 1, followed by elamipretide in Period 2.

In order to be included in the trial, subjects had to be males who are 12 years or older with genetically confirmed Barth syndrome. They had to be ambulatory but with an impaired 6-minute walk distance at baseline visit at the investigator's discretion, and they had to be on a stable medication regimen for 30 days before the baseline visit.

They would be excluded if they met any of the following criteria: if they had an inpatient hospitalization within 30 days prior to the baseline visit; or were undergoing an apparent pubertal growth spurt; or had a history of heart transplantation or were waiting for a heart transplant; or if they had an implantable cardioverter defibrillator discharge within the 3 months prior to baseline or were expected to undergo device implantation during the trial.

There were two primary endpoints, the distance walked in meters during the 6-minute walk

test and the average of daily total fatigue score on the Barth Syndrome Symptom Assessment over 7 consecutive days prior to the study visit. These endpoints in subjects who received elamipretide were compared to those who received placebo after 12 weeks of treatment. The applicant used Hochberg's procedure to control family-wise type 1 error rate at 0.05.

The Barth Syndrome Symptom Assessment is a patient-reported outcome questionnaire that assesses symptoms of tiredness, fatigue, and muscle weakness using 8 or 9 questions, depending on the version. Each question has five response categories. The responses are scored 1, not at all, to 5, very severe.

The applicant used the total fatigue score which is comprised of the responses to the following three questions on the symptom assessment tool: Question 1, tiredness at rest; Question 2, tiredness during activities; and Question 4, muscle weakness during activities. The total fatigue score responses range from 3 being the best score

to 15 being the worst. Lower scores reflect less symptoms. Sixteen patients were screened with 12 patients being enrolled and completing Part 1. The median age for all subjects was 16.5 years. There were 4 adults and 8 children.

This table shows the 6-minute walk test results. Pre-dose baseline results are on the first row. The results of the primary endpoint are on the second row. The mean distance walked by the subjects who received elamipretide was not statistically different from those who received placebo. This table also shows an additional analysis of the change from the pre-dose 6-minute walk distance to the end of treatment period. There is no significant difference between the two groups. Notably, a mean placebo effect of approximately 30 meters was observed.

As previously mentioned, the total fatigue score ranges from a best score of 3 to a worst score of 15. This table shows primary endpoint results for the total fatigue score. As shown in the first row, the baseline total fatigue score was

7.7 in the elamipretide arm and 7.4 in the placebo arm, reflecting a mild to moderate degree of tiredness and muscle weakness. As shown in the second row, the mean score improved in both the elamipretide and placebo groups with no statistically significant difference between groups.

This table shows additional analysis of the change from the pre-dose total fatigue score to the end of treatment period. There is no significant difference between the two groups.

This table shows the secondary endpoints that were planned to be tested within type 1 error control. The secondary endpoints are listed in the first column and the least square mean change from baseline is listed in the fourth column. Subjects in both study arms showed some improvement on hand-held dynamometry and SWAY balance score; however, the nominal p-values were not statistically significant for any of these secondary endpoints. In addition to the secondary endpoints, an exploratory endpoint of the Caregiver

Global Impression also did not show a significant change between the two treatment arms.

This table shows results of the exploratory endpoint of cardiolipin ratio. There was a small decline in cardiolipin ratio in both treatment arms with no significant difference between the groups.

I will now summarize the key takeaways from SPIBA-201, Part 1. First, SPIBA-201, Part 1 was an adequate and well-controlled trial. It did not show statistically significant differences between elamipretide and placebo on its primary endpoints of 6-minute walk test and the total fatigue score. Second, there was no alpha left to test any secondary endpoints. Lastly, a mean placebo effect of approximately 30 meters on the 6-minute walk test was observed. The placebo effect will be discussed in more detail by my colleague, Dr. Bai, later in the presentation.

Now, I will discuss SPIBA-201, Part 2 or the TAZPOWER Extension. This was a single-arm, open-label extension of Part 1 to evaluate safety, tolerability, and longitudinal trends in the

efficacy of elamipretide. This schematic shows the design of SPIBA-201, Part 2. The first visit in Part 2 occurred at week 12, 12 weeks after the end of Part 1 end-of-study visit.

In order to be included, subjects had to have been compliant with treatment in Part 1 and appropriate to continue in Part 2 for the investigator's assessment. There were no exclusion criteria. Ten of 12 subjects from Part 1 consented to participate in Part 2. The primary objective was to establish the long-term safety and tolerability of elamipretide up to 192 weeks. For efficacy, the applicant planned to describe longitudinal trends over the same time period of up to 192 weeks.

The endpoints were the following: the 6-minute walk test; the total fatigue score; the mean muscle strength by hand-held dynamometry; 5 times sit-stand test; and 2- and 3-dimensional echocardiographic measurements; balance score from SWAY application balance assessment; patient-reported outcomes such as Patient Global

Impression scales, Clinician Global Impression scales, Caregiver Global Impression scales; and biomarkers.

This table shows the disposition of the subjects who participated in SPIBA-201. Ten subjects enrolled in Part 2 after completing Part 1. Two of these subjects discontinued participation in Part 2 due to adverse events. Eight subjects participated in Part 2 up to and including week 168, but only 3 subjects participated in Part 2 up to and including week 192. There was also one subject who discontinued elamipretide at week 72 but remained in Part 2 until week 192.

While the primary endpoint was safety and tolerability, the focus of our presentation is efficacy; therefore, we will discuss descriptive results of the secondary efficacy endpoints. The applicant conducted multiple analyses such as the change from baseline, which was the pre-dose value in Part 1, to several weeks that were pre-established in the protocol.

This table shows a change from baseline in some of the efficacy outcomes during Part 2. The first column on this table lists the efficacy outcomes. The second column lists the pre-dose value for that outcome from Part 1. The rest of the columns show the change from pre-dose baseline during various timepoints in Part 2.

On face, the magnitude of change from baseline in some outcomes, particularly the 6-minute walk distance and the hand-held dynamometry, appear notable. For 6-minute walk distance, the mean baseline was about 380 meters and the mean increase was about 60 meters at week 12 and about 90 to 100 meters at the other timepoints. For the hand-held dynamometry, the mean baseline was about 130 newtons and the mean increase was about 38 newtons at week 12 and ranged about 40 to 60 newtons at the other timepoints.

While these changes seemed a lot larger than what was seen on average with placebo in SPIBA-201, Part 1, all patients in this extension study knew with certainty that they were receiving

elamipretide, so we have concerns regarding the interpretability of these changes on effort-dependent motivation biased endpoints. Also, the impact of pubertal changes such as growth spurts, and increase in muscle mass, and familiarity with the repeated testing procedures over 3 years, or 168 weeks, is difficult to determine; therefore, it is difficult to infer that these changes reflect a treatment effect of elamipretide.

As noted previously, there was one subject who discontinued elamipretide at week 72 in SPIBA-201, Part 2, then remained in Part 2 until week 192. Off elamipretide, his hand-held dynamometry results increased from baseline by 50 newtons at week 96, 24 weeks after stopping elamipretide, and by 38 newtons at week 168, 96 weeks after stopping elamipretide. This example shows that someone who is not on elamipretide could increase their hand-held dynamometry with the range reported by subjects who were receiving elamipretide.

This graph shows the actual 6-minute walk distance at each assessment in Part 2. The X-axis lists the visits starting at the Part 1, Period 1 baseline. The Y-axis shows a mean distance walked on the 6-minute walk test by all subjects at each assessment.

There is an increase of 6-minute walk distance compared to baseline at each visit and as shown in the table on the previous slide; however, when we consider the week 12 6-minute walk distance at SPIBA-201, Part 2, of 443 meters, indicated by the red arrow, which the applicant reports is nominally significant with a p-value of 0.02 compared to baseline, this 6-minute walk distance is essentially the same as the 443 meters walked both by the elamipretide- and placebo-treated subjects at the end of SPIBA-201, Part 1, which we know was not significantly different between groups with a p-value of 0.97.

So we question one of the findings at week 12 in Part 2 would have deferred from placebo had the study continued in a randomized,

double-blinded fashion to this timepoint. Similarly, we have difficulty reliably concluding that the other timepoints reflect a true treatment effect in this open-label extension study.

In our assessment, the open-label, single-arm design of SPIBA-201, Part 2, with all subjects aware that they were receiving elamipretide, can introduce performance bias on the effort-dependent endpoints, meaning that the subjects knew they were receiving active treatment, and they might have expected that they would improve, and this could impact the extent of the exerted effort.

In addition, SPIBA-201, Part 2 had no control arm to distinguish changes seen with elamipretide from known confounders such as the extent of effort, growth and muscle development related to puberty, and unknown confounders. In summary, the changes in the effort-based endpoints in Part 2 cannot be reliably interpreted as a treatment effect of elamipretide in patients with Barth syndrome.

The applicant also included several patient, clinician, and caregiver-reported outcomes in Part 2. One among them was the Patient Global Impression of Symptoms, where subjects rated the severity of the Barth syndrome symptoms that they experienced over the previous week on a 0-4 scale, ranging from zero, no symptoms, to 4, very severe symptoms. The applicant also used the Clinician Global Impression of symptoms. Here, clinicians assessed the severity of their patients' Barth syndrome symptoms during visits on a 0 to 4 scale.

At week 168, a nominally significant change from baseline was reported in both scores. In subsequent slides, I will explain why these changes cannot be reliably interpreted as a treatment effect of elamipretide; however, I will first discuss video assessments that were also performed.

As a supplement to SPIBA-201, the applicant obtained interviews of SPIBA-201 subjects and their caregivers, or observers, after at least 12 weeks of open-label extension to explore their perception of change and experience during SPIBA-201, Part 1.

Subjects and caregivers, or observers, were asked to select an interview partner such as a family member or a friend to read interview questions and film the video interviews. If the subjects were unable to find an interview partner, they could conduct the interview themselves by flipping their smartphone camera towards themselves.

The interview was divided into 8 modules that discussed different aspects of changes in subject functioning during the trial, such as life before elamipretide; daily life today; fatigue and weakness today; other aspects of Barth today; elamipretide treatment Period 1; washout period, and treatment Period 2. In these videos, a majority of the patients and caregivers reported improvements such as increased energy, stamina, muscle strength, appetite, heat tolerance, and improved wound healing. Some of the reported improvements occurred during the placebo treatment period.

We do not think that the changes in the patient outcome assessments, like the PGIS, total

fatigue score, PROMIS Fatigue score, or clinician outcome assessment like CGIS can be interpreted as a treatment effect of elamipretide. We note that during the randomized placebo-controlled Part 1, there was no statistically significant difference in these PROs between the elamipretide and the placebo groups.

Furthermore, in Part 2, there was no control arm, and we are concerned about the open-label design that could lead to a biased assessment of how subjects feel knowing they were receiving elamipretide. With regard to the video assessments, these are difficult to interpret due to the potential for recall bias. It is also unclear whether responses were affected by subjects being unblinded in Part 2 when the video assessments were recorded.

Cardiolipin ratios were measured at various timepoints in Part 2. This table lists the change from the pre-dose baseline. The pre-dose baseline mean cardiolipin ratio was approximately 19. The largest observed mean decline from baseline was

approximately 17 with mean declines typically in the 5 to 10 range. Note that the cardiolipin ratio is approximately 100-fold greater in patients with Barth syndrome compared to normal controls; therefore, the magnitude of the observed changes from baseline at various weeks in Part 2 appear small and is of unclear clinical significance.

In our assessment, the changes in the cardiolipin ratio in Part 2 are difficult to interpret for the following reasons. First, while an elevated cardiolipin ratio is diagnostic for Barth syndrome, there are no data to support a relationship of longitudinal decline in cardiolipin ratio with clinical outcomes in patients with Barth syndrome. Second, without a control group, the changes in cardiolipin ratio are difficult to interpret. Furthermore, as mentioned previously, no improvement in the cardiolipin ratio was observed with elamipretide in an animal model of Barth syndrome.

In summary, SPIBA-201, Part 2 was a single-arm, open-label, uncontrolled study. The

results of the various effort-based endpoints and PROs are difficult to interpret as treatment effect of elamipretide due to the potential bias and adequate control.

Now, we will discuss SPIBA-001 or the natural history control study. SPIBA-001 was designed to generate evidence of efficacy of elamipretide because SPIBA-201, Part 1 did not find statistically significant differences and because of limitations of SPIBA-201, Part 2. Its title is a long-term study to evaluate the efficacy of elamipretide compared to a retrospective natural history control in subjects with Barth syndrome. In this study, outcomes from SPIBA-201, Part 2 were compared to an external natural history control. The primary endpoint was a change in the 6-minute walk distance from the pre-dose baseline to weeks 64 and 76. The secondary endpoints were muscle strength by hand-held dynamometry, 5 times sit-stand test; SWAY application balance assessment; and the multidomain responder index.

The two groups being compared in SPIBA-001

were the treated set and the natural history cohort. The treated set was comprised of subjects from SPIBA-201, Part 1 and Part 2. The natural history cohort was comprised of subjects with available data for age, height, and baseline 6-minute walk distance and at least one post-baseline, 6-minute walk distance.

The data for the natural history cohort were collected prior to the inception of SPIBA-001 by the principal investigator for SPIBA trials under independent clinical research activity. The natural history cohort was comprised of patients with Barth syndrome who attended the interdisciplinary clinic at the Johns Hopkins Kennedy Krieger Institute and the Barth Syndrome Foundation's International Scientific, Medical, and Family conferences held in 2014, 2016, and 2018. Propensity score methodology was used to try to balance the two study arms.

With respect to the study design of SPIBA-001, there were several important differences in the timing and number of endpoint assessments

between the two groups being compared. In the treated set, the endpoint assessments were conducted according to the schedule of assessments of SPIBA-201. In the natural history cohort, retrospective results of study endpoints were used when available. Some of these assessments were conducted under independent investigator-led research protocols. Results from the treated set and the natural history cohort were available before SPIBA-001 was designed.

We note that patient-level results of subjects who comprise the natural history cohort for 6-minute walk test and some echocardiographic parameters were published in 2016, and additional patient-level results for the 6-minute walk test were published in January 2019 prior to the finalization of the SAP for SPIBA-001. The rationale for the selected timepoint of week 64 and 76 to evaluate study endpoints was not provided.

In 2019, the FDA informed the applicant that we did not agree with the design of SPIBA-001 to evaluate the treatment effect of elamipretide. The

rationale was that the 6-minute walk test is effort-dependent, has high intra-subject variability, and is difficult to interpret based on comparisons with an external historical control group, especially given the lack of statistically significant results obtained in the randomized, placebo-controlled SPIBA-201, Part 1.

This flow chart describes the composition of the treated set. Twelve subjects participated in SPIBA-201, Part 1. Of these 12 subjects, two declined to participate in SPIBA-201, Part 2; therefore, 10 subjects formed the treated set in SPIBA-001. Two of these 10 subjects discontinued their participation by week 64. This left 8 subjects in the treated set by week 76 of SPIBA-001.

This flow chart describes the composition of the natural history cohort. There were 79 subjects with Barth syndrome in the research database. Nine of these subjects were excluded because they had participated in SPIBA-201. An additional 27 were excluded because they were younger than 12 years of

age. Four subjects were excluded because they had received heart transplant and another 20 subjects were excluded because they did not have the required data. This left 19 patients from the research database who had covariate data and at least one post-baseline 6-minute walk test, forming the natural history cohort in SPIBA-001.

Before we discuss the results from SPIBA-001, note that no subjects in the natural history cohort, and only some subjects in the treated set, had primary or secondary endpoint assessments available at week 64 and 76; therefore, extensive imputation was used to estimate data for the primary and secondary endpoints for the treated set and the natural history cohort at week 64 and 76. Of note, imputation is a statistical technique that replaces missing data with estimated values. We will discuss additional details of the limitations of imputation in subsequent slides.

This table shows that using imputed endpoint values, the treated set had a larger change from baseline in their 6-minute walk distance compared

to the natural history cohort at week 64 and 76. The natural history cohort did not show any improvements. This table shows that using imputed endpoint values, the treated set had larger changes from baseline in these secondary endpoints compared to a natural history cohort at week 64 and 76.

In summary, the subjects in the treated set are subjects from the open-label, single-arm extensions, SPIBA-201, Part 2. Using these data in an externally controlled study cannot resolve the potential bias that exists due to knowledge of treatment assignment on effort-dependent endpoints. In addition, there are several statistical limitations of SPIBA-001 that will be discussed next.

Given these limitations, it is unclear if the results of SPIBA-001 can be interpreted as a treatment effect of elamipretide. We also note that no patient-level data for cardiolipin ratio from the natural history cohort was submitted.

Now, my colleague, Dr. Bai, will present the statistical assessment.

FDA Presentation - Steven Bai

DR. BAI: Good morning. I'm Steven Bai, a senior statistical reviewer in the Office of Biostatistics at FDA. I will present from a statistical perspective on some limitations of the efficacy data collected in this application. Before I dive into details, I would like to acknowledge my colleague, Dr. Jae Joon Song, for his contribution to the assessment of the propensity score method used in the natural history analysis.

The review team has identified a number of limitations in the application, which include the use of effort-dependent endpoints with knowledge of treatment assignment as a primary efficacy endpoint, inadequate control of potential selection and confounding bias, and the adequacy of using 100 percent imputed data for the primary efficacy analysis. First, I will discuss the issues associated with the use of an effort-dependent endpoint. Let's revisit what was observed in the randomized, double-blind portion of SPIBA-201.

Six-minute walk distance results at the end of the treatment were similar in subjects receiving either elamipretide or placebo.

Let's dive a little deeper into this placebo effect. In Period 1, the subjects receiving elamipretide showed a mean improvement of 40.9 meters. Subjects receiving placebo showed a mean improvement of of 59.6 meters. Note, this placebo effect of 59.6 meters in 12 weeks was the largest improvement in 6-minute walk distance among four changes from pre-dose list in this table. We also note that in Period 1, all 6 subjects on elamipretide experienced injection site reactions, which may have contributed to the functional unblinding. In Period 2, those initially receiving elamipretide showed small improvements after switching to placebo, while those initially receiving placebo still showed noticeable improvement after switching to elamipretide.

Here is a visual illustration of individual subjects' 6-minute walk distance trajectories in both sequences and both periods. The subjects in

the blue box are everyone who had elamipretide during Period 1. From the trajectories, we can see everybody except one subject improved their 6-minute walk distance from pre-dose to week 12. Similarly, the subjects in the red box are those who took placebo during Period 1. Here, we can see every subject improved their 6-minute walk distance from pre-dose to week 12, with the greatest observed improvement being 91 meters.

During Period 2, the blue box highlighted the most subjects who initially received placebo and crossed over to elamipretide, again improved in 6-minute walk distance after switching; however, the red box highlighted that most subjects who initially received elamipretide and crossed over to placebo did not improve in 6-minute walk distance after switch.

It is well documented in literature that the assessment of effort-dependent endpoints in an open-label study or in settings where inadvertent unblinding is highly likely can result in bias, the magnitude of which we typically do not know. Also,

effort-dependent assessments can be confounded by environmental and motivational factors, which tend to be uncontrolled in open-label, single-arm studies. An example of a confounding environmental factor is fatigue from traveling to the clinic, and an example of a confounding motivational factor is expectation bias in overly optimistic patients.

Secondly, in SPIBA-201, Part 1, a sizable placebo effect on 6-minute walk distance was observed, and no statistical significant difference between elamipretide and placebo on 6-minute walk distance was observed. It is unclear whether SPIBA-201, Part 2 changes reflect a treatment effect of elamipretide in the absence of a control arm and because of performance bias in open-label assessments. In addition, as previously discussed, similar concerns apply to other effort-dependent endpoints.

Now, I will discuss limitations regarding the control of potential selection and the confounding bias. In SPIBA-001, external control from natural history data was constructed to assess

the treatment effect of elamipretide. Among a total of 79 subjects in the long-term natural history data, 19 external controls were identified.

Recall that more than half of subjects were excluded during the process due to various reasons discussed earlier. Such elements of the study design caused two distinct types of potential biases. First is the selection bias arising from considering a sub-sample of subjects in the natural history data as controls. Subjects' attributes likely to influence the primary endpoint might differ among subjects selected into the sub-sample or not. The second is confounding bias arising from lack of treatment randomization. In other words, subjects' attributes likely to influence outcomes might differ among subjects in the treated set and external control.

It is important to make clear distinction between the two sources of bias because in SPIBA-001, both types of biases might arise simultaneously, and the statistical method to mitigate one type of bias should not be expected to

address the other.

In SPIBA-001, propensity score method was applied to balance baseline covariates between the treated set and the natural history control. When done correctly, such method can help with controlling the confounding bias; however, such method cannot address the impact of potential selection bias arising from considering a sub-sample of subjects in the natural history data as control. Furthermore, propensity score methods cannot address other study design issues such as impact of lack of blinding, especially when the endpoint is effort-dependent with a high intra-subject variability.

Also, there were a few limitations of propensity score method applied for confounding control in SPIBA-001. First, the propensity score method was not prespecified. The covariates for the propensity score model should have been prespecified in the statistical analysis plan to increase confidence in the interpretation of the study results. Also, the propensity score model

only considered the baseline measures of age, height, and the 6-minute walk distance.

With a limited number of measured covariates, the statistical inference will most likely be subject to bias from unmeasured confounding. Some unmeasured confounders might include heart functions, motor development, and the pubertal status. These clinical characteristics might affect whether a subject meets the eligibility criteria to receive treatment, and it can also be associated with the efficacy endpoint. Another concern is that the study sample size was not sufficient to use propensity scores. The literature suggests at least 6 to 10 treated subjects per covariate to estimate the propensity scores.

Lastly, I will discuss the inadequacy of having 100 percent imputed data for the primary efficacy analysis set. The natural history database did not contain any functional data for the natural history cohort at the timepoints chosen for the primary efficacy analysis at weeks 64 and

76.

These two panels are the spaghetti plots of every subject's actual 6-minute walk values. All the circles are the observed 6-minute walk distance for each subject. The left panel is for the natural history cohort and the right panel is for the treated cohort. The vertical lines in both panels correspond to weeks 64 and 76. As you can see from the values of the two horizontal X-axes, the natural history cohort data on the left side spanned much wider durations.

The applicant then fitted a single linear regression line for each subject based on observed 6-minute walk data. The predicted value on each regression line at week 64 and 76 were used for the natural history analysis in SPIBA-001. To illustrate the regression imputation method further, here is a subject who had four measurements as indicated in the blue triangles on the blue curve. This green simple linear regression line is generated from these four observed data points, so week 64 and week 76

values, i.e., two red dots on the screen line, then used as the imputed 6-minute walk distance at these two timepoints.

One of the key factors in having a reliable regression line is having enough observations, but the natural history cohort just has two fields of available measurements over a longer period of time. As we can see from the bar chart on the left, 5 subjects has two measurements, 9 subjects has three measurements, and 2 subjects each had 4 and 5 measurements, respectively. Only one subject has 8 measurements.

We do not know why these are the only subjects that had any post-baseline, 6-minute walk distance performed. Additionally, we do not know whether these subjects are different from the subjects who did not have any 6-minute walk distance performed. We also do not know why these observations were obtained sparsely and unsystematically.

Lastly, based on the submitted data, all except one subject in the natural history cohort,

comprised of subjects who underwent 6-minute walk distance assessments at the Barth syndrome conferences, these subjects attended at least 2 out of 4 conferences. No subject attended all four conferences.

Hence, for subjects who had more than three assessments recorded, it is unclear how these 6-minute walk distance assessments were obtained. On the other hand, the treated subjects on the right all had at least nine observed 6-minute walk distance values, and it is because they had systematic visits following SPIBA-201, Part 2 open-label protocol.

Another factor in having a reliable regression line is to have observations obtained close to the timepoint of interest, especially if the measurements have high variability, and we use week 64, which is one of the timepoints of interest, as an example. This table on the right shows that none of the natural history cohort subjects had measurements available around week 64. The average time between week 64 and the timepoint

when a preceding observation was available was 392 days, and the average time between week 64 and the timepoint when a following observation was available was 381 days.

On the other hand, the treated cohort had observation around week 64, and average gap for observations away from week 64 was 15 days with a range of 2 to 30 days. So the natural history cohort subjects have much larger time gaps between observed dates and week 64 than those in the treated cohort.

In summary, it is unclear how we should interpret analysis results based on 100 percent imputed data. We usually recommend that the amount of imputed data to be kept to a minimum so that the estimated treatment effects and interpretations, in terms of the specified estimate, are relatively unaffected by the imputation.

Second, we question the reliability of the imputed data since two key elements for having a reliable imputation based on the regression method are violated: one, having a sufficient number of

observations; and two, having them observed reasonably close to the timepoint of interest. Third, we would like to point out that only single imputation was used. We do not recommend a single imputation method due to well-known issues documented in the literature.

This concludes the statistical presentation. Now, I would like to welcome back Dr. Punnoose for the summary assessment.

FDA Presentation - Ann Punnoose

DR. PUNNOOSE: Our summary of efficacy data is what we're going to review in the next few slides. The primary endpoint results of SPIBA-201, Part 1, an adequate and well-controlled clinical investigation, do not show a treatment effect of elamipretide when compared to placebo. Second, due to the limitations discussed, we have concerns that SPIBA-201, Part 2 and SPIBA-001 are not adequate and well-controlled clinical investigations for the following endpoints, making it unclear whether there is a treatment effect of elamipretide on the 6-minute walk distance, other effort-dependent

endpoints, patient-reported outcomes, including the total fatigue score and the cardiolipin ratio.

We now turn to echocardiography data from SPIBA-201 and SPIBA-001 to assess whether there is a treatment effect of elamipretide on the echocardiographic parameters. In SPIBA-201, Part 1, the applicant compared 27 echocardiographic parameters between the elamipretide and placebo groups. There were data for 12 subjects, 8 children ages 12 to 17 years and 4 adults, ages 21 to 35.

The eligibility criteria for SPIBA-201, Part 1 did not require the presence of cardiomyopathy at baseline. Nine of 12 subjects were reported as having a remote history of cardiomyopathy and/or heart failure. Mean values of the echocardiographic parameters that characterized left ventricular structure and function were normal at baseline in all patients.

This table shows the mean values of several echocardiographic measures of left ventricular structure and function at baseline of SPIBA-201,

Part 1. These values were normal. The mean left ventricular ejection fraction was 64 percent. The mean left ventricular global longitudinal strain was minus 20 percent. The mean indexed left atrial volume was 28 milliliters per meter squared.

This table shows a change in several parameters that describe left ventricular structure and function between baseline and at the end of SPIBA-201, Part 1. There were no significant between-group differences in the change from baseline. The nominal p-values in the last column do not show statistical significance. In our assessment, these echocardiographic data from SPIBA-201, Part 1 do not show a treatment effect of elamipretide on cardiac structure or function after 12 weeks of treatment.

Now, I will present the echocardiographic data from SPIBA-201, Part 2. For the echocardiographic analysis in SPIBA-201, Part 2, there were 10 subjects. Seven were children aged 12 to 17 years and three were adults aged 21 to 35 years. According to the protocol,

echocardiographic data was obtained at select weeks. The applicant evaluated the change from baseline in multiple echocardiographic parameters at multiple timepoints and proposed that an increase in left ventricular stroke volume indexed to body surface area suggests a treatment effect of elamipretide. Hence, we discussed changes in left ventricular volumes and left ventricular ejection fraction.

First, I would like to review several definitions. Left ventricular and diastolic volume is a volume of blood left in the left ventricle at the end of diastole. Left ventricular and systolic volume is a volume of blood remaining in the left ventricle at the end of systole. Left ventricular stroke volume is a volume of blood pumped out of the left ventricle during systole.

The formula for determining the stroke volume is the difference between the left ventricular and diastolic volume and the end systolic volume as shown on the slide. Left ventricular ejection fraction is the percentage of

blood ejected during systole in relation to end diastolic volume. The formula is a stroke volume divided by the end diastolic volume multiplied by 100.

Finally, some adult and pediatric echocardiographic parameters are indexed to body surface area to account for differences related to age and body size, specifically in the pediatric age group. Echocardiographic parameters are further described using Z scores, which is a measurement of how many standard deviations the value is away from the mean. To be considered normal, a measurement must be within minus 2 to 2 Z scores or two standard deviations.

This table shows that, generally, at various timepoints, the mean left ventricular, and diastolic, and systolic volumes indexed to concurrent body surface area and the left ventricular ejection fraction remained within the normal range; however, the mean left ventricular stroke volume indexed to body surface area was slightly lower than the adult normal reference

range of various timepoints.

We will now focus on results at week 168. At week 168, the increase in indexed left ventricular and diastolic volume was more than that in the indexed left ventricular and systolic volume, while the left ventricular ejection fraction remained unchanged. Hence, the indexed left ventricular stroke volume increased. It is likely that the observed increase in indexed left ventricular stroke volume was driven largely by increases in left ventricular and diastolic volume, which can be an age-related change. I will discuss this more in the next slide.

Additionally, giving the underrated course of cardiomyopathy in Barth syndrome, indexed left ventricular and diastolic volumes can also increase if subjects transition from normal left ventricular size and function to dilated cardiomyopathy. We also note that other than left ventricular and diastolic volume, other hemodynamic factors such as blood pressure at the time of echocardiogram may have impacted left ventricular stroke volume, but

these were not reported.

In summary, SPIBA-201, Part 2 included 7 pediatric and 3 adult subjects. At baseline using adult reference range, the mean indexed left ventricular and diastolic volumes are normal. Indexed left ventricular stroke volume was low, but other measures of diastolic dysfunction were normal. Hence, we cannot conclude that subjects in SPIBA-201 had diastolic dysfunction at baseline. Furthermore, left ventricular and diastolic volume is expected to increase up to 3-fold during childhood, which may have contributed to the observed increase in indexed left ventricular stroke volume in SPIBA-201, Part 2. Thus, without an adequate control arm, the observed increase in indexed left ventricular stroke volume cannot be reliably interpreted as a treatment effect of elamipretide.

Now, I will discuss the post hoc echocardiography data analysis. The applicant conducted post hoc analysis comparing left ventricular and diastolic volumes, left ventricular

and systolic volume, and left ventricular stroke volume between subjects who had received elamipretide in SPIBA-201, in patients with Barth syndrome who had echocardiographic data available from at least one follow-up timepoint in the research database, as well as from baseline, used for the natural history cohort in SPIBA-001. The echo natural history cohort subjects were different from the natural history cohort in SPIBA-001. Only 4 patients overlapped.

This table shows several aspects in which SPIBA-201, Part 2 and the echo natural history cohort were not comparable. First, echocardiograms were not obtained per a prespecified schedule in the echo natural history cohort, and the clinical indication for obtaining the echocardiogram was not specified. We do not know if the echocardiogram was obtained for a clinical concern.

Second, there are far fewer echocardiograms obtained for subjects in the echo natural history cohort; thus, we have an incomplete understanding of the cardiac course of these patients. Third,

3-dimensional echocardiogram results were used for SPIBA-201, Part 2, whereas 3-dimensional and 2-dimensional echocardiogram results were combined for the echo natural history cohort.

Fourth, the mean age of the SPIBA 201, Part 2 subjects was 20 years, while in the echo natural history cohort was 12 years. As left ventricular volumes are known to change with age, the differences in age groups limit comparability of SPIBA-201, Part 2 and the echo natural history cohort.

Lastly, while the SPIBA-201 subjects had a reported history of cardiomyopathy with normal baseline echocardiographic measurements, there was no information available about the cardiomyopathy phenotype of the echo natural history cohort subjects. As discussed, the cardiomyopathy associated with Barth syndrome is known to have an undulating course. It is difficult to compare left ventricular volumes when the baseline cardiac phenotype is unknown for the echo natural history cohort.

The applicant conducted a mixed model repeated measure analysis to compare left ventricular volumes between the treated set and the echo natural history cohort. As shown in the table on this slide, there was no significant difference in the change from baseline in the indexed left ventricular and diastolic or systolic volumes between the treated set and the echo natural history cohort. There was a nominal increase in the indexed left ventricular stroke volume in the treated set compared to a nominal decline in left ventricular stroke volume in the echo natural history cohort; however, this comparison is difficult to interpret given the methodological limitations discussed on the prior slide.

In summary, given the major limitations of the post hoc SPIBA-201, Part 2 and echo natural history cohort comparison of echocardiographic parameters, the reported differences in the left ventricular volumes by the applicant cannot be reliably interpreted as a treatment effect of elamipretide. Furthermore, the relationship of

changes in left ventricular volumes with clinical outcomes is not known.

Putting everything together, our overall summary is as follows. The FDA recognizes that Barth syndrome is a rare, serious condition without approved therapy and has significant unmet need. The randomized, double-blind study, SPIBA-201, Part 1, did not show statistically significant differences between elamipretide and placebo on its primary and secondary endpoints. The FDA has difficulty attributing the findings from the single-arm, open-label extension study, SPIBA-201, Part 2, and the externally controlled study, SPIBA-001, to elamipretide because of significant limitations discussed today. This concludes the FDA presentation. Thank you for your attention.

Clarifying Questions to the FDA

DR. BUTLER: Thank you very much.

We will now take clarifying questions for the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if

you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all of my questions," so that we can move on to the next panel member.

Are there any clarifying questions for the FDA?

DR. ALEXANDER: I had two. One is, is there any historical precedent for using evidence from another development program as part of confirmatory evidence? And the reason I ask is because I was interested to hear from the sponsor regarding some of the results of ongoing studies in other mitochondrial deficiencies, and I just wondered if there was any precedent for including that as part of confirmatory evidence.

DR. GANDOTRA: I'm Charu Gandotra, clinical team leader. I'll be serving as moderator for the FDA. I can start. Confirmatory evidence can be considered if there is at least a single adequate

and well-controlled trial that provides evidence of effectiveness. Absent a successful adequate and well-controlled trial, confirmatory evidence cannot support substantial evidence of effectiveness.

Did I answer your question or do you have further questions?

DR. ALEXANDER: Yes, I suppose so. I mean, we've also been told that the strength of confirmatory evidence and the nature and quality of such can vary based on the strength of the adequate and well-controlled trial, but that's fair enough.

I guess the other question, I guess maybe I had conflated absence of evidence with evidence of absence with respect to some of the preclinical data, so I was going to ask the sponsor, but I suppose I'll ask you instead, and perhaps the sponsor can opine during their time later, if you could further discuss the evidence regarding the absence of improvement in cardiac structure and function in taz-deficient mice. That seems like a very important model that would be informative, and it was my understanding that there wasn't evidence

of such but, in fact, on one of your slides, if I understood, it sounded like there was actually evidence of an absence of an effect, and I just wondered if you could provide more information about, again, the effect of the product on cardiac structure and function in taz-deficient mice. Thank you.

DR. GANDOTRA: Thank you for your question. I will invite Dr. Naren Reddy Chintagari, nonclinical reviewer, to please respond. Thank you.

DR. CHINTAGARI: Hi. This is Naren Chintagari, nonclinical reviewer. Can you pull slide 27? To answer that question, the applicant evaluated the effect of elamipretide taz-deficient knockout mice model. Cardiomyopathy was induced after birth, and the cardiomyopathy was confirmed at week 8. The animals were treated for 6 weeks with elamipretide, and at the end of 6 weeks, there were no changes in the cardiac function.

Did I answer that ok?

DR. ALEXANDER: Okay. Yes, that's fine. I

just didn't know if there was more depth or nuance to that, but that's fine, and thank you very much.

DR. CHINTAGARI: Thank you.

DR. BUTLER: Dr. Kishnani?

DR. KISHNANI: Thank you. This is Priya Kishnani. I had a couple of questions. The first one was -- I don't know if I missed this -- how many in the historic-controlled group have an increase in the 6-minute walking distance? And when comparing these groups, was the impact of puberty or growth spurts accounted for both in the treated group as well as in the natural history group?

Then the other question was, given that we're trying to understand mechanism of action, was the MLCL to CL ratio also looked at in the natural history group over a period of time? I understand there are fluctuations, but was there any evidence to suggest that it was more in the treated group versus the natural history group?

DR. GANDOTRA: Thank you, Dr. Kishnani, for your questions. I can answer part of it. We were

not provided data on cardiolipin ratio from the natural history cohort subjects in SPIBA-001, and I will invite Dr. Steve Bai to comment on if any patients in the natural history control showed an increase in 6-minute walk distance. And I think the second part of that first question is whether or not effective puberty was accounted for in assessment of these measurements. Thanks.

DR. BAI: Hi. This is Steven Bai, statistical reviewer. I don't have the exact number of how many subjects improved their 6-minute walk distance, but to clarify your question, there are multiple visits. Like I said, one subject had 8 visits and some had four and five. At which timepoint are you referring to? I'll add that nobody had a visit at around week 64 and 76.

DR. KISHNANI: Yes. Even outside exact timing, I'm just trying to understand what is the variability when you're looking at it from a natural history cohort to see what the robustness of that data collection is versus the clinical trial.

DR. BAI: I don't have the number off my head, but if I do a little calculation, I can get back to you on this.

DR. GANDOTRA: Dr. Kishnani, we'll try to get that information back to you after the break.

DR. KISHNANI: Correct. And my other question really was related even to that treated group, how many had entered puberty. When we say that they had this increase up to 90 meters, et cetera, how many of them could you attribute this to a growth spurt or something else?

DR. GANDOTRA: Thank you for your question. I will invite Dr. Ann Punnoose to respond, and I will request slide 131 to be pulled up, please. Thank you.

DR. PUNNOOSE: This is Ann Punnoose, the clinical reviewer. This is a table that shows the 8 patients from SPIBA-201, and if you go from left to right, the second column is their baseline age, followed by their baseline height, and the percentile at baseline, that's followed by their age at week 168, their height percentile at

week 72 -- sorry, their height at week 72 and their percentile at week 72.

You can see in that 3-year period, several of these patients did increase their height. The biggest increase was seen in the patient second from the bottom, who went from a percentile of 7.9 to one of 25.5 by week 72. So we do think growth had an impact on their performance. In addition to just height, it could also be their muscular development and their ability to perform on the 6-minute walk test. Thank you.

DR. GANDOTRA: Thank you, Dr. Punnoose.

I'll invite Dr. Steven Bai to provide additional information, and I will request slide 80 to be pulled up, please. Thanks.

DR. BAI: Yes. I don't have the exact numbers of variabilities in terms of the 6-minute walk distance, but here's every subject's spaghetti plots in both treated cohort and the natural history cohort.

DR. GANDOTRA: Dr. Kishnani, have we addressed your questions?

DR. KISHNANI: Yes. It looks like there could be variability. That's what my real question was, and the extent of it. If I look at the one right on the top, it's anywhere from 550 to upwards of 600 meters. That's what I was trying to see, what is the extent of that variability.

DR. BAI: I don't have the number off my head, but also, for the natural history, like I said, 5 subjects only had 2 measurements. We cannot assess the variability for those 5 subjects.

DR. KISHNANI: Agreed, yes.

DR. BUTLER: Thank you.

Dr. Stein, you had a comment?

DR. STEIN: Thank you. I thought it might be worth just a comment on the question regarding confirmatory evidence because I think this is sometimes a challenging concept and worth perhaps some clarification. As you mentioned, it certainly is the case that the strength of the confirmatory evidence can vary with the strength of the adequate and well-controlled trial. As Dr. Joffe mentioned, when we have a very strong trial, we still need

confirmatory evidence that is meaningful, that is clearly supportive, but it may not need to be as strong as in this situation where the trial is not a strong adequate and well-controlled trial; still still supportive, still positive, but in that case, the extent of confirmatory evidence would need to be much more substantial.

You asked about a related indication. We can use a related indication as one method, one approach to confirmatory evidence, but I would note there that, typically, that is in a situation where we have a trial that has been completed, it's been reviewed, and typically it's in a setting where indication is granted; or that's not absolutely necessary, but certainly the trial would have to have been completed, reviewed, and confirmed that it did show the benefit. The relatedness of the indication means a shared mechanism and the pharmacology expected to be generally similar as well. That's a scientific judgment call as to how related that indication might be, but I think a key point is that this study would need to be

completed, reviewed, and confirmed that it demonstrated the efficacy in this related condition. So I think we do have to be cautious for ongoing studies where we don't yet have results.

DR. BUTLER: Thank you.

Ms. Shuman?

MS. SHUMAN: Hi. This is Devin Shuman speaking. I was hoping to have some of the FDA statisticians speak a little bit more -- admittedly because that's the area I feel like I know least about -- in terms of the concerns involving power of a withdrawal study and the feasibility of trying to get more data for this population, with the understanding there isn't a population to get 6 participants for each variant, and how long a washout period might take in terms of the feasibility of next steps.

DR. GANDOTRA: Thank you, Ms. Shuman, for your question. I will invite Dr. Steve Bai to please respond. Thanks.

DR. BAI: Can you bring up the backup slide

for 155? SPIBA-201 was designed to detect a mean improvement of 50 meters in the 6-minute walk distance, and since it was a co-primary endpoint, it also was designed to detect 1.3 points in the total fatigue score. The multiplicity was controlled by the Hochberg procedure, so either endpoint could potentially have an alpha of 0.025 to provide them with 80 percent power.

DR. GANDOTRA: In addition to this, I think you're wondering what can be done in the future in terms of feasibility in an adequately powered trial, even feasible in this patient population. We've had some discussions, and for a trial with a similar design as SPIBA-201, Part 1, that were to enroll a total of 24 subjects, a power of 80 percent to be able to detect a treatment effect of at least 30 meters on 6-minute walk distance potentially can be done.

So this is just one example. There are several other sample size considerations or estimates that have been discussed or presented in the past. One example from the sponsor side during

pre-NDA meetings also shows for a 6-minute walk distance trial endpoint, a sample size of 35 patients will have an 80 percent power to demonstrate a superiority for a mean change of 30 meters between the two arms. So there are some potentially feasible study designs that we are open to discuss further.

Does that answer your question?

MS. SHUMAN: Mostly, sort of. I think there are still questions about how much of the population we've used up already, and things like washout period, how long would that study need to happen. But that was very helpful. Thank you.

DR. BUTLER: Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor from Inova Schar. In reference to Study 201, Part 1, the behavior of the placebo patients in Sequence 1 and Sequence 2 is very different, and in my experience, very unusual. What is the FDA's explanation for the difference in the behavior of the placebo patients in the two different sequences?

DR. GANDOTRA: Thank you, Dr. O'Connor, for

that question. I'll invite Dr. Steve Bai to respond, please.

DR. BAI: Yes. Bring up slide 153. I'm not making any conclusions, but there's a notable difference in terms of age, and weight, and height between those two sequences.

DR. GANDOTRA: I think you're asking for the placebo, the difference in behavior in the two placebo arms; is that right, Dr. O'Connor? Give us one minute. We will like to pull up a slide to show those changes.

DR. GANDOTRA: Can we pull up slide 73, please? Dr. Bai, please go ahead. Slide 72.

DR. BAI: Can you repeat your question again?

DR. BUTLER: Dr. O'Connor, can you repeat the question, please?

DR. O'CONNOR: As you can see, the placebo patients, the behavior looks different in the two sequences. What's your explanation for why there's such an extreme difference in the behavior of the placebo patients in the two different sequences?

DR. GANDOTRA: Dr. Ann Punnoose, can you add?

DR. PUNNOOSE: Yes. This is Ann Punnoose, clinical reviewer. One of our considerations for the reason why the placebo behavior was different could be that by the second sequence, the patients were attuned to the injection site reactions that they were seeing with elamipretide, and knew whether they were on the drug or whether they were on placebo.

DR. BUTLER: Dr. Shaw, you had a related comment?

DR. SHAW: Yes. I just wanted to bring up a related comment to Dr. O'Connor's question. Having done a lot of trials in chronic conditions, symptoms can vary in severity. This is not that unusual a pattern in some settings, in my experience. Sometimes we call the statistical effect regression to the mean, and it relates to when folks decide to join a clinical trial when their disease is varying, and in many settings, it can be when they're having a worse than usual

experience that they're particularly motivated to join a clinical trial.

So in some settings, I'm not saying that's a perfect explanation, but it can happen; that in that initial period, everybody improves because they joined the trial at a time when their symptoms were a little more severe. That effect has happened, so it doesn't necessarily happen again in a second period. So in crossover trials, you can sometimes see this difference. I can't say in this particular instance, but it's one theory people have put forward for patterns like this.

DR. BUTLER: Do you have another follow-up comment?

DR. BAI: Yes. Can you go to 73? One of the possible reasons, if you look at the left panel, the elamipretide/placebo sequence, not everybody dropped back down to their pre-dose level after washout, and that could be a contributing factor why we don't see any placebo effect in Period 2. On the right side, you can see pretty much everybody, after 4 weeks of washout, they

pretty much went back down to their original pre-dose level.

DR. BUTLER: So we have a hard start for the open public hearing at 1:15 and not a flexibility there. I recognize that there are more questions for the FDA as well, but similar to the previous session, there is another session after lunch where we can ask clarifying questions both to Stealth and to the FDA.

So I suggest that we will now break for lunch. We will reconvene again in this room at 1:10 so that we can get ready at 1:15 sharp. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break, and we will reconvene at 1:10. Thank you.

(Whereupon, at 12:18 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

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

(1:15 p.m.)

Open Public Hearing

DR. BUTLER: Why don't we go ahead and get started? We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you, at the

beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals of today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect; therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

We have many speakers in this open public hearing session. Please limit your comments to 4 minutes or less. If you speak for more than

4 minutes and if I interject, this is not out of any disrespect, but only to give the other speakers their due time.

Speaker number 1, please step up to the podium and introduce yourself. Please state your name and any organization you are representing for the record. You have 4 minutes.

MR. BURGER: My name is Walker Burger, and my travel has been supported by the Barth Syndrome Foundation. I'm a patient of the TAZPOWER study and currently in the compassionate use program. For 27 years, Barth syndrome controlled everything I did, but now I am living the life I could only dream about before.

I was diagnosed with cardiomyopathy and low muscle tone as an infant and was diagnosed with Barth syndrome at 19. Growing up, physical activities had to be modified. Something as simple as walking was a challenge for me. I was driven around summer camp to save my limited energy, as I couldn't even walk a quarter of a mile without stopping. I just simply could not participate with

my peers. After graduating from college, I was able to work full time but had absolutely no energy to do anything else.

In August of 2017, the TAZPOWER study began, and on my way to the study site, I was running late to catch a flight. I needed to run to the gate, but my legs just simply wouldn't let me. My heart was pounding. I arrived as they were closing the gate with tears in my eyes, full of disappointment and frustration. I was randomized in the double-blind study of elamipretide, not knowing whether I was on placebo or drug.

Gradually, after receiving the study drug, I began having more energy. I was able to come home from work and not go straight to bed. My energy, strength, and attitude continued to improve. I was able to walk further with fewer breaks and had the energy to meet friends after work. I was just happier and more pleasant to be around. I was enjoying life more. Even people at work that had absolutely no knowledge at all of the trial commented that I seemed to be more energetic,

happier, and less tired. I never had so much energy in my entire life.

I still do not know, to this day, if I was on active drug, but my guess is I was. I eventually had to go through the washout portion of the trial, where I gradually was completely back to my old self: tired, weak muscles, drained of energy, and very frustrated. The momentum and strength were gone, and I also became depressed. At the end of the trial, I looked forward to resume the drug in the open-label extension. During this time period, I gradually regained my energy and strength.

Now, for 7 years on the study drug, improvements I have seen in my strength, energy, and quality life, and continue to see uninterrupted, as I now am able to exercise 4 times a week for 90 minutes and have more energy than I have ever had in my life.

In summary, if someone were to ask me today if I have the symptoms of Barth syndrome, I would say, "No. I had the symptoms of Barth syndrome."

Thank you.

DR. BUTLER: Thank you very much.

Speaker number 2, please step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record. You have 4 minutes.

DR. RANDELL: Hello. My name is Dr. Jay Randell, and my travel expenses and support were supported by the Barth Syndrome Foundation. I am here today with my 21-year-old sons, Justin and Michael, who were both diagnosed with Barth Syndrome at the age of 2. Justin presented with congestive heart failure at birth and was placed on cardiac medications immediately, then followed by cardiology afterwards. Michael's symptoms did not show until his first bout with congestive heart failure at 20 months old when he passed out in preschool and was admitted to the pediatric ICU with an 8 percent stroke volume on a milrinone drip. We were terrified we might lose him.

In 2017, at age 14, Justin and Michael entered the trial for elamipretide and have

currently been taking the medication through the open-label extension ever since. This medication has helped them so much that they have begun to take their ability to function normal for granted. As parents, we worried about the return of congestive heart failure during the adolescent growth spurt, but the boys' echocardiograms were stable throughout the period, and they didn't show what was normally known as decline during puberty.

Justin had a long bout dealing with nocturnal enuresis into his mid-teens. No other therapies worked. Elamipretide was pivotal in helping the muscular control develop there as well. In phase 1 of the study, it was clear that Justin, age 14, was on drug first. Within a few weeks, he stopped wetting his bed. Then when the brothers switched the study arms, it became obvious when his bed wetting gradually returned that he was not on active drug. Once he went back on drug during phase 2, the bed wetting stopped again.

Michael, at age 16, had a job at Safeway collecting carts and bagging groceries. He had

become accustomed to feeling and functioning well. Unbeknownst to us as parents, he had decided to stop taking his injections. After being off drug for 3 weeks, he became weak, had pain in his abdomen, and was bedridden. In the emergency room, the EKG revealed irregularities in his ST segment. He had to quit his job and missed a week of school. Afterwards, he started drug again.

MR. J. RANDELL: My name is Justin Randell. Ever since I've been taking elamipretide, it has helped me with my daily activities. I work as a full-time barista at Starbucks, and I'm on my feet and work at a rapid pace. A few years ago, it was difficult for me to take my daily dose. Now that I have been taking my shot regularly, I can feel the difference. I can keep up with my peers, both work and socially, eating has been easier, and I can consume more, allowing me to gain weight.

MR. M. RANDELL: Hello. My name is Michael Randell. I work full time in the produce department at Kroger, lifting heavy loads daily. I work out at the gym 3 to 4 times a week and attend

Metropolitan State University of Denver. I also maintain a normal social life. All of my activities require physical strength that would not be possible without the medication. My appetite has increased significantly, enabling me to have a physical strength that I need to be successful in all these activities and enjoy a relatively normal life.

MR. RANDELL: Elamipretide has been pivotal in giving my sons the ability to live productive and enjoyable lives. This is the only medication that they take and are on no other medications to support the various systemic inadequacies that tax their systems due to the poor function of the mitochondria without elamipretide. I am pleading before the FDA to make this life-saving medication available to our Barth community. Thank you.

DR. BUTLER: Thank you.

Speaker number 3, please step up to the podium and introduce yourself. State your name and any organization you're representing. You have 4 minutes.

MS. BOWEN: My name is Shelley Bowen, and I'm the Director of Family Services, an advocacy for the Barth Syndrome Foundation. Neither I nor any of the Barth Syndrome supported speakers have received funding from industry to participate in this meeting, and the Barth Syndrome Foundation has paid for travel for me and most of the speakers. We have also worked with Larry Bauer from Hyman, Phelps, and McNamara as a regulatory consultant. I am also here as a mom and hope no other family has to go through what our family has gone through, but as Kate mentioned earlier, since 2014, 18 percent of our U.S. community has died.

On my son's, Evan, 4th birthday, he realized he was different. All his friends hopped onto the chairs for birthday cake, all by themselves, without any problem, and that's something that any 4 year old should be able to do. Evan tried, and he tried, and he tried, and he just didn't have the strength to get up on the chair. He refused my help, and it was agonizing to witness to see him push me away for help. He finally looked around

the table, and he saw all the other 4 year olds sitting there ready for the birthday cake, and he just flung himself to the chair, utterly defeated.

Seven months later, he went into heart failure, and one morning I went to the grocery store. When I got back, he was lying on the floor next to the door. He wanted to go with Mommy, but he just wasn't fast enough to get to me to let me know. Imagine walking through that door and seeing your kid, that you know has cardiomyopathy, lying on the floor.

For a moment, I froze, and then temporarily I felt relief because suddenly I realized he wasn't dead. But all of that changed because I said, "Evan, why are you here?" And he said, "I wanted to get to you, but I just couldn't move." And that's when terror really struck into my heart. That was when I knew that it could end. And tragically in 1990, before his 5th birthday, he suffered a massive stroke, and my beloved son died. He was gone forever. That was my first deep dive into Barth syndrome.

In the years following, my son Michael, Evan's brother, was also diagnosed with Barth syndrome and developed cardiomyopathy. Michael kept needing stronger and stronger drugs to treat his cardiomyopathy. Each of them had risks of exciting his proarrhythmic heart or being cardiotoxic. By 2009, he couldn't make it through a semester of college classes without excessive absences and lengthy hospitalizations. He was listed for a heart transplant that very same year.

For 5 months, he would look out the window of his hospital bed, and he would see the helicopters land on helipad, and he was wondering if the person in that helicopter, whose life was at risk, was the one that could save his life. It was the warped existence for him, and it took a toll on his psyche.

Just 2 days after Michael's 23rd birthday, all hopes of the future for Michael were gone, and Michael died waiting for a heart that never came. He never measured his life by days, but rather by what he did in the days he had. The last minutes

of his life were all about the wait. If he were here today, he would be here instead of me, pleading for the option to try a therapy that would fill the days with opportunities rather than existing and waiting.

In addition to the data that you have heard today, parents and people that I know who are taking elamipretide have told me again and again that this drug is making a real-world difference in their lives. Parents would rather have the choice to give their child the therapy to improve their life rather than, me, choosing to end life support. Please approve elamipretide for our community, and use your maximum flexibility and your decision making, and please give us hope. Thank you.

DR. BUTLER: Thank you.

Speaker number 4, please step up to the podium and introduce yourself, your name and any organization you're representing. You have 4 minutes.

MR. MANN: My name is Benjamin Mann, and my travel has been supported by the Barth Syndrome

Foundation. I am 27, and I have Barth syndrome. My mother's family has lost three boys to Barth syndrome. Throughout my life, I have attended funerals of numerous Barth friends, including my 24-year-old cousin who had Barth syndrome. At 3 weeks old, I was on life support, and my parents were told I would not survive.

My life is not normal; endless doctor's appointments, medicines, physical, speech, and feeding therapies. I didn't walk until I was two and never rode a bike. My school years were difficult, no sports, no gym class, frequent illnesses. I required having a defibrillator nearby and a daily personal school-ed nurse. I was bullied because of my size, and I was depressed.

Barth has wreaked havoc on my body. My symptoms have included an enlarged poor pumping heart and left ventricle noncompaction; cyclic neutropenia; muscle wasting, fatigue, and daily muscle pain. I'm on multiple medications that do not fix me. In February 2023, I woke up and could not feel the right side of my face or arm due to

having a stroke. November 2023, I was back in the hospital in severe heart failure and my abdomen full of fluid. I have never feared death like that. Doctor said a heart transplant was likely needed.

I came home wearing a cardiac life vest in fear of arrhythmia. Desperately wanting to live in avoid transplant, my parents and I requested for compassionate use of elamipretide. Here's a comparison timeline since my stroke and starting elamipretide.

Prior to my stroke, I worked a 30-hour a week office administration job. I went to the office 1 to 2 days a week and struggled walking from the parking garage, which was only a block away. After two hospitalizations, my fatigue increased, pain intensified, muscles wasting, depleted energy, and no appetite. I had no strength to even get out of bed. Having to sit down while showering, which I had never done, I worsened to the point I could no longer work. I had absolutely no energy to walk. My only outings

were to doctor's appointments, and I had to be wheeled everywhere I went.

In May of 2024, I started daily elamipretide injections. My parents began noticing I was out of bed more, going to the kitchen to snack and cook for myself, and not eating in the bed. I have more stamina to go to the pool, lake, and hiking, along with many other things that I was not able to do before. I was uncertain about attending our Barth conference in July, but with my improved energy, it allowed me to travel and attend.

The most I ever weighed was in high school at 118 pounds. After my stroke, I had no appetite. The basic task of cooking a simple meal I could no longer do. At 6 foot 1, my weight dropped to 90 pounds. I have been on elamipretide for about 5 months now. My weight is back up to 110 lbs and my appetite has improved. For many years, my heart function was stable with an ejection fraction of 35 to 40 percent. My stroke caused my heart function to decline to an EF of 15 percent and showed severe noncompaction. Since elamipretide, my recent

August echo shows my heart EF has improved to 30 percent and moderate noncompaction.

Elamipretide has helped me to have more energy, less muscle pain, and improved my quality of life. Please consider the impact elamipretide has had on my life. Discontinued use would be devastating to me. Every Barth individual deserves this targeted treatment. Approval of elamipretide would mark a critical turning point for all affected individuals with Barth syndrome. Thank you.

DR. BUTLER: Thank you very much.

Speaker 5, please introduce yourself, name and any organization. You have 4 minutes.

MS. STRAWSER: Hi. My name is Michelle Strawser, and my travel was supported by the Barth Syndrome Foundation. I am the mother of Clint, who is 25 years old living with Barth syndrome. He was diagnosed at the age of 14. When Clint's Barth syndrome diagnosis came, we finally had an explanation for his physical limitations, and now he was different from his siblings and other

children. Yet, it also came with the fact there were no treatments for his devastating illness.

Clint had muscle weakness since birth and developed slowly. He didn't walk until he was 2 years old and has always had extreme fatigue. He could not run, play any sports, ride a bike, jump on a trampoline, even walk around the mall with his teenage siblings and cousins. We tried to send him to school, but he wasn't physically able to handle getting on and off the bus, much less walking around school all day. He also missed too many days from being sick and having to stay in bed due to fatigue, so we had to home school.

Clint had to use a wheelchair to do any outings that consisted of walking more than a block, and at the age of 16, he couldn't even carry a gallon of milk. He was depressed with his world basically confined to the four walls of his room; however, Clint saw a glimmer of hope when he was given the opportunity to participate in the elamipretide study.

When the study started, Clint was randomized

to be on either the drug or the placebo, and at one point during the clinical trial, we went out to dinner as a family. Out of habit, we took an Uber even though the restaurant was only 4 blocks away. While after eating, we walked out, his dad and I were talking, and I looked up, and Clint was walking ahead of us. I just started crying. I had never seen him walk ahead of me before at that pace. He was actually able to walk all the way back. Clint told me he could feel it in his body and in his muscles. He was completely astonished at how it felt to walk like that and for that long. He had never felt that much energy before.

After 12 weeks, the study required him to start the 4-week washout. Within days, he felt his energy drain and the extreme fatigue come right back. He was once again confined to the 4 walls of his room, and the only outings were to doctor appointments. Once the open-label period started, Clint was back on the drug again, and his life totally changed. He's been on the drug now for 7 years, and he consistently has the strength and

stamina to cook gourmet meals, he can play and babysit his nieces and nephew, and he no longer has to use his wheelchair.

Clint has always had a passion for woodworking. Before the drug, he wasn't able to do it because of his extreme fatigue and muscle weakness. Now, he has been able to do his woodworking and has opened an online store to sell his creations. The ability to make things and accomplish something with his talents has changed his whole outlook on life. This has given him independence to earn money and contribute to society. This drug has not only helped him physically, but mentally and spiritually.

Now, he is facing the devastating possibility that this drug will not be available to him, and his life will go back to the way it was before the drug. Clint fears losing his independence, his ability to earn a living, and being able to do the things with his family and friends. It's not imaginable to live without the benefits of elamipretide, which has now totally

changed the course of his life, and this drug has given him a newfound freedom and zeal for life. Thank you.

DR. BUTLER: Thank you.

Speaker number 6, please, if you can come to the podium and state your name and organization. You have 4 minutes.

MR. WILSON: My name is Jacob Wilson, and my travel was supported by the Barth Syndrome Foundation. I am a 24-year-old affected male with Barth syndrome, and I'm out here to share my experience with elamipretide and the importance it had in my life. When I started elamipretide at the age of 17, I could have never guessed the strides I would mentally and physically take. This medicine made me feel like a new person.

From a young age, I realized that things were never going to be quite as easy as for others. This all changed thanks to this amazing trial. I took elamipretide 6 days a week and was amazed at the wonders it brought me. I could have never guessed the amount of positivity it brought into my

life. The feeling alone of waking up refreshed was a sign that my life was going for the better. I had new dreams to aspire that had once been seemingly taken away by my own health.

Within 6 months on this medication, I gained weight, strength, and stamina. I gained 25 lbs. That was a miracle for a guy who has never been able to gain weight. I felt like a completely different person. I was happier and more motivated in life. While I was on this medication, it took me from the bottom of the energy spectrum and ignited the smoldering stove I once had. I could walk blocks without tripping over my inverted feet or gasping for air.

My parents saw a child that couldn't tie his shoes without sitting now walk blocks in the city never before thought of. I could finally lift my feet off the ground fully, unlike previously where I would drag my heels. These are the things most people overlook, the little things we are blessed to be able to do every day. We can live with the diagnosis; it's the daily battles that count for

us.

Elamipretide was the key to opening doors to normality for myself. It gave me the will and want to go out and make friends and do activities that were not possible before. I have the newfound confidence that I will not burn myself out for the next week over a day of fun. It was almost as if I had a new life, a new body, a new mind. I got to enjoy fishing, hunting, and all of the other things that were impossible before. I can't explain enough half of our battle is our energy. Simply walking and eating are incredible tasks, especially before I started taking elamipretide. I understand this isn't a cure-all, but the improvements I saw were important to me.

I am no longer on the medication due to personal health concerns, and it has been a true battle. I personally can say that life off of this medicine has been a constant struggle, from having a feeding tube placed, to losing all energy and weight that I had previously gained. That still doesn't shun my hope for this medication, and I

would be forever grateful to have a chance to be on it again. Thank you for your time.

DR. BUTLER: Thank you.

Speaker number 7, please state your name and if you're representing an organization.

MS. DUBUQUE: My name is Jamie Dubuque, and my travel was supported by the Barth Syndrome Foundation. I am the mother of Declan Comerford, a Barth syndrome affected toddler. On December 31, 2022, at 11 months old and weighing only 11 pounds, Declan was admitted to the Children's Hospital of Philadelphia after experiencing cardiac arrest. He was ill beyond our understanding with severe dilated cardiomyopathy, had an ejection fraction of 18 percent, and placed on an ECMO heart-lung bypass machine because his heart function was not enough to sustain his life. He was diagnosed with Barth syndrome 2 weeks later.

When we learned of Barth syndrome, it felt as though there couldn't be a worse possible sentence for our baby. We had an answer finally for why he was born small and not keeping up with

his milestones, and why he had gotten so sick. We were informed by his team that for Declan to survive to the heart transplant that he needed to go home, he required a left ventricular assist device. His LVAD surgery was 5 days before his 1st birthday.

At this time, we were offered the rare opportunity to receive elamipretide under the Expanded Access Program. We said yes to the trial drug as we faced the unfortunate reality that elamipretide was our only option. He started on the drug just a day later and came off of ECMO. As his hospitalization continued, Declan received a great deal more than we expected from his daily treatment of elamipretide. Over the course of his hospitalization, Declan excelled in his physical therapy and his occupational. He was more energized than we had ever seen him, gaining weight, and his always increasing endurance was very noticeable.

On May 1st, at just under 16 weeks on elamipretide, a routine echo showed that Declan's

heart was back to normal size and function. His ejection fraction had improved from 18 percent to 54 percent. After transferring to our home state of Arizona in mid-July, Declan's LVAD was successfully explanted at Phoenix Children's on August 2, 2023. At that time, he was on elamipretide for an estimated 28 weeks and on the LVAD for 26 weeks. He was going home with the heart he was born with. He would be the first known Barth child on an LVAD and transplant list to achieve this recovery.

Since Declan's discharge on August 21, 2023, not only does his heart remain at a normal function and ejection fraction, he himself functions like a normal, healthy little boy. His cardiologists have pointed out that if they didn't have knowledge of his history while looking at his heart, they could not see any signs of heart failure and would not have guessed he had Barth syndrome. Today, he is thriving at 25 lbs, almost 3 feet tall, and kicking life's butt. He is strong physically and mentally because Barth just isn't holding him back the way

it once did. No longer having elamipretide is just not an option for Declan. His health will decline, and he will face the limitations from cardiac disease he once had.

Imagine the life that the affected boys of the future will have before them if they all had access to elamipretide as early on in diagnosis or even sooner than Declan. Imagine Barth syndrome diagnosed routinely in the beginning when the heart is just beginning to fail and having the chance to be saved like Declan. Please make elamipretide available for our community. It would be nothing short of devastating if I had to watch Declan's body decline and his full life start to shrivel to even half of what it is today. Thank you.

DR. BUTLER: Thank you.

Speaker 8 is virtual. Please unmute yourself, and turn on your webcam and introduce yourself. You have 4 minutes.

MR. HOLLY: Good afternoon. My name is Ben Holly, and I do not have any financial support, but I'm here to represent Barth syndrome. I was asked

to speak about elamipretide, as I was a participant in the drug trial. I was diagnosed with Barth syndrome prenatally after my older brother passed away undiagnosed with Barth syndrome. I have six other older siblings, five sisters and one brother, who are not affected by Barth symptoms. My parents had never heard of Barth syndrome until my brother passed away, though a lot of research and having my brother's tissue tested, my mom discovered that he had Barth syndrome, and I was tested prenatally and was diagnosed.

I started the elamipretide drug trial in August of 2016 when I was 12 years old. I am now 20. When I first started the drug trial, I didn't feel any different, as I still felt tired and didn't think it was helping. I later realized that I must have been on the placebo for the first 12 weeks. After 12 weeks, the second phase started, and I'm now sure that I was put on the actual drug. Eventually, I became more energetic, and I ran down the street to my friend's house. That's when my mom knew that I was taking the

actual drug and not the placebo.

I have been taking the drug since the second phase of the drug trial for about 7 years. Before taking elamipretide, I was not very active and struggled to keep up with my peers in school, especially in PE. I would be very fatigued and didn't have much energy. I would often fall just due to walking because of the weakness in my legs. I missed a lot of school due to the lack of energy and frequent illness. After I finished 6th grade, I began homeschooling so that I could work on school when I had the energy and did not have to worry about missing so much school in a public school setting.

Since being on elamipretide, I have experienced sustained improvement. When I turned 16, I began working in the pro shop at our county golf course. At that point, I'd been on elamipretide for 4 years, and I regularly work 20 to 30 hours a week, along with doing my high school courses online. The days that I worked, I was able to walk anywhere from 10,000 to

12,000 steps in a day, washing gas golf carts, and served the golf course members.

Today, I'm attending a very rigorous 9-month mission apprentice program, where I attend school 8 hours a day, Monday to Friday. Outside of school, I study, prepare homework for the next day, as well as work on service projects. After 9 months in school, I will go to a mission field for about 14 months, either in the states or a foreign country. I'm really concerned that if I have to stop taking elamipretide, I may lose all the progress I have made and have to change my plans. I don't believe that I could be as active and involved without it.

I would not have been able to accomplish any of this without the benefit of elamipretide. I feel like by having the benefit of this drug, I'm able to live a much fuller and active life than I would have without it. I would love for all my Barth brothers to be able to have access to this medication so that they can have a full and active life also. I really hope that elamipretide is

approved so that I can continue to enjoy the benefits that it provides for me. I can't imagine a life without it. Thank you for considering approving elamipretide. I appreciate your time.

DR. BUTLER: Thank you very much.

Speaker 9, please introduce yourself.

DR. ELSHARKWAI: My name is Ibrahim Elsharkwai. I'm a pediatric biochemical geneticist at Mount Sinai in New York. My travel here was supported by the Barth Syndrome Foundation, and I have no relevant financial disclosures.

In January 2024, the NICU metabolic genetics and MFM teams all met with an expecting mother to discuss a worrisome and grim prognosis. At 33 weeks and 3 days gestation, this fetus was noted to have Barth syndrome with a known familial pathogenic variant and worsening cardiomyopathy. So the initial fetal echo at 22 weeks gestation, about 10 weeks prior to this meeting, was notable for early signs of cardiomyopathy with then mild right ventricular dysfunction and mild tricuspid regurgitation. By January 2024, at the time of

this meeting, at the time of this multidisciplinary family visit, the fetal echo was notable for noncompaction of both the right and the left ventricles with moderate to severe depression of both ventricles.

Now, several factors shaped this into a grim prognosis. There are no FDA approved therapies for Barth syndrome, no disease modifying therapies whatsoever. The family history in this patient was also notable. The parents had had another son who did not have an abnormal pregnancy with abnormal fetal echo such as this one but developed heart failure symptoms after birth and required a heart transplant at 6 weeks of age. As such, the fact that this pregnancy was already notable for fetal cardiomyopathy earlier in gestation, and to such a severe degree, did not lend itself to any optimism.

The cardiovascular and cardiothoracic surgeons had determined that to even be considered for ECMO or transplant, the infant would need to reach 37 weeks of gestation where ECMO could be a bridge to a possible LVAD. At this point, I

discussed the risks and benefits of the investigational drug, elamipretide, with the family, and given the limited side-effect profile, the absence of any other targeted therapies, both the parents and the FDA approved the use of elamipretide via emergent IND in this patient.

The baby was born at 36 weeks 4 days gestation. We initiated elamipretide a few days later via IV daily infusion, which would later be transitioned to a subcutaneous form a few months later. Initially, not much was different than the original prognosis. The baby's cardiovascular function was severely depressed, and early echocardiograms demonstrated an ejection fraction of 19 percent at 2 days of life. All the usual standards of care were continued along with elamipretide, and for a time, the baby required intubation and mechanical ventilation, vasopressor support with multiple agents, and the course was complicated with sustained ventricular tachycardia and arrhythmias. He was listed as status 1A for heart transplant. To put it mildly, this baby was

very sick.

By May 2024, however, the baby had demonstrated both clinical and radiographic improvements. Ejection fraction was now stable in the 40s. He was on room air. He was tolerating daily elamipretide without any notable or apparent adverse effects. He was downgraded on the transplant list, and most importantly, he was able to go home.

Since he was discharged from the ICU to home on May 7, 2024, he has continued elamipretide at home in once daily subcutaneous form without any issues at all, not so much as an infusion site reaction. His most recent echocardiogram on September 10th demonstrates ongoing improvements in his ejection fraction and other parameters, and he is now delisted for transplant.

To the best of my experience and knowledge as a triple board certified physician, I would not have expected this baby's trajectory to change as it has without elamipretide. This baby has thrived against initial expectations. Medical management

with a promising investigational agent in the absence of any other available treatments proved safe in this growing baby, associated with sustained, measured, and observed improvements in clinical and radiographic benchmarks. Thank you.

DR. BUTLER: Thank you very much.

Speaker 10?

MS. HALL: Good afternoon. My name is Amie Hall, and my travel has been supported by the Barth Syndrome Foundation. I am the caregiver for my three Barth syndrome sons. My son Robert passed away from the effects of Barth syndrome at 3 years 9 months, Ian is 35 years old, and William is 24 years old. William and Ian have both struggled through life with their disease. They have never been able to compete in sports, band, school, or even everyday life that their peers, that are considered typical, can do. Sorry.

William and Ian both dreamed to participate in the elamipretide trial. Unfortunately, Ian did not get chosen to participate due to some abnormal readings on his Holter monitor test. William,

however, was able to participate. During the drug trial, when William was on elamipretide, he had a better quality of life than he had prior to the trial. William gained weight. He had increased appetite; had increased energy; more pattern sleep routine; less fatigue during walking; less joint and muscle pain; a better attitude on life; and better overall health. While on elamipretide, William gradually gained 20 pounds.

William went off elamipretide in May of 2019 to give his abdomen a break. While on the trial, he was also taking GCSF injections, which is also administered in the abdomen. William only has two quadrants of his abdomen that he can take injections in due to scarring from his feeding tube that he had when he was younger. Since stopping elamipretide, William has lost weight and is currently 6 feet tall and weighs 85 lbs.

William has lost his appetite; has increased lethargy; has increased muscle and joint pain; has a hard time doing simple household chores; and has become very weak. His outlook on life has

decreased catastrophically. William recently said he would rather be dead than continue to live the life he is currently living. William also had to drop out of Pittsburgh Institute of Aeronautics and was not able to finish his training to become an avionics technician. After going off elamipretide, William's health has constantly declined, and he no longer has the stamina to complete his training. He was scheduled to complete his final semester when he had to cease his training.

Ian would like to begin taking elamipretide when it becomes available and is approved by the FDA. Ian is very excited about the positive results that William had and believes his quality of life will increase exponentially when he is able to go on elamipretide.

Due to William's health issues, my husband and I both work jobs so that we are able to continue to help support our sons. My sons would both be able to work and support themselves if they were able to be on elamipretide. They would have less pain, less fatigue, and overall better health

and nutrition. As a parent, I hope that elamipretide will be approved for use. Thank you.

DR. BUTLER: Thank you very much.

Speaker number 11, please.

MS. KARLE: Hello. My name is Jordan Karle, and my travel has been supported by the Barth Syndrome Foundation. I am mother to my 8-month-old son, Jaylen, who stands beside me today, and big sister to my brother Jonathan, both affected by Barth syndrome. Jonathan unfortunately passed from Barth syndrome on April 2, 2004 at only 18 months old. I was too young to remember the details, the trials and tribulations, fear, anger, and hurt that came with my brother and his Barth syndrome, but I do remember them all with my son Jaylen.

Before Jaylen was born, I was seeing the heart transplant heart failure team monthly, if not more. During prenatal echocardiograms, they noticed the left side of his heart was enlarged. His left ventricle did not function properly. It also had a small leak due to it not being able to open and close properly. He had thickening on the

left side of his heart as well. Every fetal echocardiogram I had, it felt like the news got worse as my pregnancy progressed. I was preparing myself, my family, and my two daughters, ages 5 and 1, to lose Jaylen before he even had a real chance at life.

At 36 weeks pregnant on February 8, 2024, at 5:37 PM, Jaylen was born. Our joy was short-lived. On February 9th at 9 a.m., Jaylen was transported to Children's Nebraska. They had placed Jaylen on high-flow oxygen, partially sedated Jaylen, and placed a UVC and a UVAC through his umbilical cord, and started him on the highest doses of milrinone and epinephrine they could.

Jaylen had labs drawn every 2 hours. Around 4 p.m. that day, they told me things were not looking good for my son. They decided to intubate Jaylen but feared during his intubation his heart would stop, and they would not be able to resuscitate him, giving him a 40 percent chance of survival. Then I heard seven of the most heartbreaking, gut-wrenching words. Would you like

to sign a DNR? I knew Jaylen was a fighter and immediately refused. I specifically remember asking the surgeon, "Are you telling me to say my goodbyes to my baby?" I also remember screaming and crying, telling him, "Please do everything you can to save my son."

After 3 hours in the operating room, Jaylen was successfully intubated. During Jaylen's stay at the hospital, prior to starting elamipretide, he was intubated and extubated twice due to his poor heart function. He had two blood transfusions, was on high-flow oxygen many times, and had an NG tube placed. We were also in the process of having Jaylen put on the LVAD and the transplant list.

Jaylen's team and I made the decision to try one final thing before transplant, and that was elamipretide. March 12, 2024, Jaylen started taking elamipretide, and it changed everything. Jaylen's heart function has been normal for 5 months. His lab work is all within normal range. He has more energy throughout the day. He is right on track with his weight and height, weighing

16 pounds, eating directly from a bottle, and now starting pureed foods and loving every second of it. Jaylen is on track with rolling over, sitting up, and many other things. Elamipretide made this possible.

Jaylen and many other of his Barth brothers deserve to not live in fear of death or transplant due to this terrible disease, but rather to live a long, beautiful life with family and friends and experience things other children get to experience without having to fight so hard for it. Please make elamipretide available for them. Not having access to this drug could be a potential death sentence to my son. Thank you.

DR. BUTLER: Thank you very much.

Speaker number 12?

DR. REYNOLDS: Good afternoon. My name is Dr. Stacey Reynolds. I'm an occupational therapist, and I serve as Professor and Director of Research at Virginia Commonwealth University in the Department of Occupational Therapy. I've been conducting research within the Barth syndrome

community for 14 years, and I think I can provide a unique insight into their occupational functioning and their quality of life.

Barth syndromes is characterized by profound and relentless fatigue. The fatigue is not just about being tired at the end of a long day; it's a form of exhaustion that permeates every aspect of their life. The more severe the fatigue, the greater the functional limitations, not just for the individual, but for the entire family. And while Barth syndrome individuals look normal, their struggles are frequently misunderstood because the depth of their fatigue is invisible to others.

This fatigue manifests itself in both physical and cognitive ways. It's the reason a young boy might stop wearing a hooded sweatshirt because something as simple as the extra weight on their back becomes unbearable. It's why someone might feel immobilized when trying to carry a bag to the airport, or even just across a room. During a qualitative research study, one individual said, "I wasn't able to move. I wasn't even able to

carry my own body, let alone carry my girlfriend's bags to the airport."

The physical and social impacts are profound and greatly alter normal, healthy childhood development. One individual shared that as a child, he would watch from the sidelines as other boys played soccer at school. He could not join in, and that not only limited his physical engagement, but his social life as well. This is more than just fatigue; it's a barrier to friendships, community, and connection.

Barth fatigue severely diminishes quality of life. One family member described it as an unforeseen illness that robs the individual of their joy and sense of self. Every day is a balancing act, deciding which activities of daily living they can complete. "Am I going to take a shower or brush my teeth? I cannot do both."

Our objective research data supports these narrative comments. Using actigraphy, my research team has measured energy expenditure in individuals with Barth syndrome, and the results are striking.

Those with Barth syndrome showed significantly lower energy output compared to control participants, and when their fatigue peaks, they cannot just push through it. They have to stop everything that they're doing, including moving. We were able to objectively define and identify the stopping behavior, which we called a crash, and these crashes significantly distinguished Barth individuals from control subjects. And I want to be really clear that this is not the type of fatigue that motivation or optimism associated with the placebo effect could possibly overcome.

Our data further supports that this constant cycle of extreme fatigue and recovery takes an enormous toll on their independence and overall well-being, and this can be compounded by the psychological toll that comes with feeling trapped inside of a body that cannot keep up with the mind's desires. Since members of the community have been taking elamipretide, I have seen things for the first time ever. I've seen babies with Barth syndrome hitting their developmental and

weight milestones. I'm hearing about adolescents who do not regress during puberty, and I'm seeing adult men who are on elamipretide who are working full-time jobs. This is something that has never even been a possibility for this community.

In conclusion, I urge you to recognize the profound nature of Barth syndrome fatigue and its serious impacts on life. It's not just a symptom; it's a barrier to independence. By understanding the invisible weight of fatigue, we can ensure that this community receives the treatment, compassion, and resources that they deserve. Having the new treatment, elamipretide, available to alleviate fatigue would make an incredible difference in these individual's lives. Thank you.

DR. BUTLER: Thank you very much.

Speaker number 13, can you please unmute yourself and turn on your webcam? Introduce yourself.

DR. GOLDSTEIN: Hi. My name is Dr. Amy Goldstein, and I'm from the Children's Hospital Philadelphia Mitochondrial Medicine Program.

Is my slide showing?

DR. BUTLER: Yes.

DR. GOLDSTEIN: Thank you.

I'm presenting a patient that I took care of here at our hospital, and this is at the time an 11 month old who came in was very ill and was not diagnosed with Barth syndrome at that time, but became very sick because he had contracted colds from rhinovirus and also tested positive for enterovirus, and was having some feeding issues, so was underweight and was delayed in some motor milestones. But because of this viral infection, became very lethargic, was minimally responsive, and presented to an outside hospital in respiratory distress and was very unresponsive, and became so distressed that he needed CPR and needed to be intubated.

His blood sugar at that time was 10, and he was quickly transported to our hospital and was found to be in severe heart failure. He had an ejection fraction at that time, which was estimated at less than 25 percent and then later confirmed to

be 18 percent, and he was then put on ECMO. We suspected at that time that he most likely had a diagnosis of Barth syndrome from some biochemical information. He had 3-methylglutaconic acid in his urine, organic acids. We were able to do some rapid genetic testing on him and confirm that he indeed had Barth syndrome.

At that time, because of his severe heart failure, I did start calling around to some of my colleagues and touched base with Dr. Hilary Vernon in Baltimore, and asked her if I would be able to enroll him in any clinical trials, and at that time he was actually too ill to be transported anywhere else.

I was running, at that time, a trial for elamipretide here for adults with mitochondrial myopathy, not for Barth syndrome, but I knew that I could call and talk to the FDA about getting emergency access for elamipretide once I confirmed his mutation, but Dr. Vernon asked me to talk to some of the cardiologists familiar with Barth syndrome, so I touched base with Reid Thompson, I

touched base with Brian Feingold, and what we talked about was the fact that even though cardiomyopathy is a feature of Barth syndrome, at that point in time, this baby was so sick, he was on ECMO, he was quickly going to be headed for needing an LVAD, and at that point, he needed so much support, and he was already needing such instrumentation that I was told he was either going to need a heart transplant or he wasn't going to make it.

So at that point, we applied for emergency access to elamipretide. We were granted access within 24 hours, and he was started on elamipretide the day after he was given his genetic diagnosis. He had a little bit of a bumpy road after that, but he was eventually extubated to oxygen and nitric oxide, and that was quickly weaned, and he was then on room air.

About 5 months later, his ejection fraction was back to 54 percent. He was on standard heart failure medication at that point, but he was stable enough to get transported back to home. He was not

from the Philadelphia area. He went home with his LVAD, but in a short amount of time, his LVAD was explanted and he was off the transplant list. He's now doing great. He's now 32 months old, and his case report is now published, and he's doing wonderfully well, still on elamipretide. So this was proof to me that this medication works, and we hope that you think so, too. Thanks very much for your time.

DR. BUTLER: Thank you very much.

Speaker number 14, if you can kindly unmute yourself and turn on your webcam.

DR. FEINGOLD: Yes. Hello. Thank you. My name is Dr. Brian Feingold. I appreciate the opportunity to speak. More than 3 years ago, I served on an advisory board for Stealth but have no current affiliations with Stealth. I'm currently a member of the Barth Syndrome Foundation, Scientific and Medical Advisory Board. I have no other relevant disclosures.

So undoubtedly by now, the committee has heard a lot about Barth syndrome and the data on

elamipretide. As a practicing pediatric cardiologist for almost 20 years, who heads the Heart Failure and Transplant Program at UPMC Children's Hospital Pittsburgh, I have cared for 9 individuals with Barth syndrome. For an ultra-rare disease, this is quite a lot and, honestly, I'm not sure if we've just been lucky or astute in our diagnosis to have had this many patients in our care.

What I can tell you is that all but one of these individuals presented as babies with severe heart failure. One was transplanted in infancy, one listed but able to come off the transplant list, and two others were transplanted in childhood or adolescence. Multiple had persistent heart failure early in life and experienced improvement in heart failure and heart function, on continuous IV infusions, with transition to oral heart failure medicines.

Some have remained stable into early adolescence, while others have had worsening heart failure and ultimately required transplantation.

As an aside from my prepared remarks, I think it's been amazing to hear some of the improvements that patients have experienced on elamipretide from the cardiovascular perspective. The patients I've cared for were earlier before elamipretide was available, so this is really fascinating to me.

That said, even after transplantation, individuals with Barth syndrome continue to face serious health risks like rejection or the need for re-transplantation, on average between 10 and 25 years after a transplant, so transplant doesn't cure Barth. And they continue to have daily fatigue and exertional limitations from Barth's skeletal muscle involvement, issues with poor weight gain and vomiting, not to mention severe neutropenia and the potential for overwhelming infection. All of this is to say that Barth syndrome results in the chronic symptoms that adversely affect quality of life, and it results in chronic medication use to address symptoms but not the underlying mechanism of disease.

Among the published findings on elamipretide

treatment for Barth syndrome, I've been most impressed with the gains on the 6-minute walk test observed during the open-label extension trial. I use the 6-minute walk test frequently in my clinical practice to try to obtain and serially follow an objective measure of activity tolerance. In none of the patient cohorts I care for, including individuals with pulmonary hypertension, Fontan circulatory failure, and cardiomyopathy with heart failure, is there a group, or even an individual that I can recall, who has shown the magnitude of improvement seen in the OLE elamipretide study. Improvements of 16 to 25 percent from baseline up to an average of 95 meters of improvement in walk distance are truly astounding.

This is not due to a test/retest phenomenon or some placebo effect related to treatment. I've had patients perform this assessment multiple times for years and have never seen this magnitude of gain. I've also put many patients on heart failure or pulmonary hypertension medications and have

never seen this magnitude of gain. Coupled with improvements in grip strength and fatigue scores, these all speak to an obvious benefit of elamipretide, given over a sufficient exposure time, on Barth skeletal muscle function, offering an improvement in the most persistent symptom complex for individuals with Barth syndrome, that of muscle pain and fatigue.

Quite frankly, medications for pulmonary hypertension were approved largely on the basis of improvements in 6-minute walk test distances of equal or less magnitude that were able to be tested in larger randomized-controlled trials. The trials that we'd love to have for Barth syndrome are just not feasible given the rarity of the condition. The drug has an excellent safety profile with injection site reactions being the most notable side effect and no life threatening or potentially life-threatening adverse effects.

So to continue to be caught in a catch-22 loop, where data on clinically meaningful benefit exists and the adverse effects are relatively

trivial in a population that is begging for an opportunity does not make sense to me. Thank you again for the opportunity to speak.

DR. BUTLER: Thank you very much.

Speaker number 15, if you can kindly step up to the podium.

DR. HALNON: My name is Nancy Halnon. I'm a pediatric cardiologist and heart transplant specialist treating infants and children with cardiomyopathy, neuromuscular, and genetic diseases. I have no relationship to the applicant. I did have some travel sponsored by the Barth Syndrome Foundation.

I'm going to present a patient. My patient is a former full-term male infant born to a mother with limited prenatal care. He initially appeared well, except for a gallop rhythm prompting an echocardiogram on the first day of life, which demonstrated severely diminished biventricular systolic function with a left ventricular ejection fraction of less than 10 percent.

By the second day of life, his BNP was

severely elevated and he developed progressive tachypnea and worsening lactic acidosis necessitating intubation and cannulation onto VA ECMO. His acidosis improved, and he was decannulated after 6 days, but without any improvement in the left ventricular systolic function. Mitochondrial disorder was suspected, and rapid genetic testing confirmed a diagnosis of Barth syndrome. Given that there's no approved treatment for Barth syndrome, he was referred to us for a heart transplant evaluation, which we completed, and he was listed.

When he arrived at our center, he was about 2 weeks old. He was on very high-dose milrinone. He was requiring non-invasive respiratory support. He was re-intubated within about a week of arrival at our hospital in the setting of severe metabolic acidosis. Thereafter, he had multiple failed extubation attempts associated with progressive hypoxic hypercarbic respiratory failure and profound lactic acidosis and very poor functional reserve. He required not just mechanical

ventilation but was heavily sedated much of the time, as well, to reduce metabolic demand and acidosis.

Given his desperate clinical state -- unstable, awaiting a heart transplant, a neonate -- we looked for additional options to treat Barth syndrome. Critically ill neonates with ultra-rare disease and listed for heart transplant would not normally have any options for participation in clinical trials, but we requested treatment with elamipretide through open-access trial for compassionate use.

He received regular daily dosing finally, starting at about age 2 and a half months. After he was on the elamipretide for about 3 weeks, he was finally tolerating less sedation, and we could engage in some regular ventilator exercise. By 4 and a half months old, after 2 months of regular dosing, he was weaned from invasive mechanical ventilation, he was successful, and acidosis crises didn't recur. Importantly, he had no side effects from the elamipretide.

At just over 5 months of age, he underwent heart transplant. In contrast to his unstable neonatal course, he had an unremarkable intra-operative and post-operative course, and rapidly extubated following surgery without any difficulty. He did well with physical and occupational therapies and continues to do well as an outpatient. It was noteworthy, then, that his clinical status improved rather than decline while he waited for a transplant, despite his heart never demonstrating appreciable improvement in his ejection fraction on serial echocardiograms.

The explanted heart demonstrated severe end-stage scarring with extensive fibroelastosis, which wouldn't be expected to support any kind of functional recovery; therefore, we feel that his overall improved clinical course prior to transplant was aided by the elamipretide and not because of myocardial recovery. Early in this course, severe metabolic acidosis crises were difficult to manage and required mechanical ventilation with sedation and chemical paralysis;

that he was breathing spontaneously and engaged in feeding. Occupational therapy/physical therapy at the time of the transplant improved his recovery from surgery and allowed some degree of normal development, for which our team and his mom are very grateful.

Clarifying Questions to the Applicant and FDA

DR. BUTLER: Thank you very much.

This concludes the open public hearing portion of the meeting, and we will not take any more comments from the audience. I really want to thank very much all the participants of the open public hearing. Sorry for the pain and the difficulty for the family members that presented their perspective, and also appreciate everybody limiting to their allotted time.

We will now take clarifying questions for the presenters. We have a lot of questions, both for the FDA and for the sponsor, so my request is for the committee members to ask succinct questions, and if the responses can be equally succinct as well, that will be very helpful. When

acknowledged, please remember to state your name for the record before you speak and direct your question to a specific person. If you wish any slide to be pulled up, please give the slide number; and then it would be helpful if you can say at the end of the question, "Thank you," and when you are done.

We will start first with the questions that were leftover for the the sponsor.

Dr. Soslow?

DR. SOSLOW: Thank you. My questions, I actually have a lot. Jon Soslow, Vanderbilt. I'm going to limit them to two, just addressing the cardiac outcomes, which I've been struggling a little bit with.

The first is on stroke volume. There are some very known increases in stroke volume with age, and there's also an inverse relationship with heart rate, and I did not see that you corrected for either of those. I'm curious if you've looked at that. I'm also curious why you chose stroke volume and not something like cardiac output, which

would take into account the heart rate changes.

MS. McCARTHY: Thank you for the question. I'm going to ask my my colleague, Dr. Carr, to come to the podium. I will say that the stroke volume data we showed you was adjusted for concurrent BSA. That was not the prespecified analysis, but it was a post hoc conducted at the request of the agency, so we did do that adjustment for growth. We also know that stroke volume is actually expected to decline in Barth syndrome with age.

Jim, can you take the rest?

DR. CARR: We don't have a slide to address heart rate. It was looked at, and the heart rates were essentially the same. This population tends to have a high heart rate anyway. Again, we looked at it, and I wish I had a slide to talk about this, but there was really no meaningful change in heart rate. Cardiac output, we did derive cardiac output. In fact, we used to have a slide to talk about that, and it was simply stroke volume times heart rate, and it was a very crude measure, as I'm sure you can appreciate.

DR. SOSLOW: The other question I had, it seems like we're hanging our hat on the Chowdhury paper for stroke volume in terms of outcomes, saying that as the stroke volume gets better, or if it gets worse at a slower rate, that these patients will live longer. But I'm curious. In that paper, there were three other metrics out of the 11 that they associated with mortality. One was LVIDd, one was LVEDV, and one was LVESD, and all three of those, as they got larger, those patients had an increased mortality.

So it seems like there's just as much, if not more, data to suggest that this may be making these kids worse, and I'm just curious how you address that.

MS. McCARTHY: Yes. I don't think we're trying to point to the Chowdhury paper for outcomes. We don't know what elamipretide's effect on long-term outcomes might be, and nor are we making any speculation about that. Really what we're looking at is the expected decline in stroke volume, whether it's rapid ahead of an acute event

or whether it's just a gradual decline over time.

Dr. Carr?

DR. CARR: Your concern is very much appreciated, in fact, it's what prompted the pretty intense interrogation of the data. Like you, seeing an increase in diastolic volume, one does have to be worried about whether that's pathologic, is that a reflect of the dilation.

As has been talked about, there were many, many echo parameters that were part of this investigation, the exploratory analysis. There was never a suggestion this is pathologic in any of those measures. I alluded to troponin and NT pro-BNP, so certainly NT pro-BNP was not suggestive; in fact, these patients are worsening. We looked at different diastolic dysfunction parameters. So as I'm sure you can appreciate, one would expect some abnormalities starting to occur on other echo indices, and we did not detect that.

So our belief is that the the volumes are low at baseline. We think this is actually a favorable change, but I do appreciate the fact that

one does have to worry about whether or not it was a pathologic finding or not.

MS. McCARTHY: We can also call on Dr. Towbin, who is still available on the line for a little bit, for another perspective on that, if helpful.

Dr. Towbin?

DR. TOWBIN: Hello again. I traveled to one meeting, was supported by Stealth Pharmaceuticals, and that's the only support I've gotten from them. I've been a pediatric heart failure transplant specialist for 35 years, and I have been an early believer in Barth syndrome and have published 11 papers over the years, eight of which have been genetic and protein based, and the remainder have been clinical. I was the first to term the disorder an undulating phenotype many years ago now and have been involved in many clinical and basic research studies, including a lot of the genetic studies.

So the question, I'd like for you to rephrase it for me so I could give you a specific

answer.

DR. SOSLOW: Sure, Jeff. It was regarding the increases in LV size, and specifically the LVEDV; and then looking at the data published by Chowdhury that showed that increased LVIDd, LVEDV, and LVESD were all associated with mortality in their review of the population.

DR. TOWBIN: Yes. So part of the problem with those studies is they're on the older patient population. A very high percentage of patients that I've seen over the years have been the babies, and they're the ones that have the undulating phenotype most typically, but they're also the ones who die fast. So when you look at that cell group, they go from very dilated to hypertrophic with limited dilation, and then undulate back to the dilated treated type and get into worse and worse heart failure.

Pre-drug therapies of the better heart failure type, but also without drugs that are specific for mitochondrial function, they just didn't do very well. The ones that did survive and

went on to become older patients, they don't have the undulating phenotype much, so you don't see the same data points as you do in the babies, and you don't have the same outcomes from the standpoint of late deaths versus early deaths.

As you heard a minute ago from Brian, there's a big difference in what we're hearing and seeing from the prior trials with elamipretide compared to pre that drug. You heard from the families the huge differences they see in a pretty short period of time and the lack of serious side effects, so at the end of the day, you end up with a real need. There are no therapies for this type of mitochondrial disorder, which is total body. It's not just cardiac, as you heard.

So the need for this drug is pretty clear-cut to those of us who have to actually take care of these patients, and they'll ultimately need it in the neonatal group as well. So this really would be the first demonstration before being able to get FDA approval to go the lower age range, which will be even more critical.

DR. SOSLOW: Thank you for clarifying that. I thought it was a median age of 7 with a range up to 22 years, but that does answer my question. Thank you.

DR. BUTLER: Thank you very much.

We have many questions, so, again, request as succinct answer as possible.

Dr. Honarpour?

DR. HONARPOUR: Thank you. Narimon Honarpour from Amgen. I have a question for the sponsor. I believe Jim Carr would be best to provide the response. This is a technical feasibility question.

We've heard a perspective on what it would take to generate additional evidence in this patient population earlier from the agency. I wonder if we could get your perspective, the sponsor, as to the technical feasibility of doing additional evidence generation in the form of a randomized clinical trial in Barth syndrome patients and what you believe we might learn from that additional evidence.

MS. McCARTHY: Yes. I'll answer the question for ease of time. Thank you for the question. We have been working for 10 years or so in the setting of Barth syndrome, and for the last 5 years have discussed almost a dozen different protocols with the agency to generate additional evidence in new trials. Many of those randomized-controlled trials, many of those proposed to be conducted prior to approval, or at least some; and the consistent feedback that we've received has been really concerns expressed about powering for many of these studies.

We've also proposed postmarketing trials when we were exploring accelerated approval. Dr. Gandotra referred to one of those studies where we were looking at a 35-patient postmarketing trial. That would have required a global trial. We conducted extensive global feasibility, and we thought we could get that done, but it would take quite a long time to recruit, requiring centers in many, many countries worldwide. And quite frankly, there's some economic feasibility ramifications for

that, as well as the sponsor.

So I think we felt that we had really explored the limits of feasibility and were unable to satisfy some of the expectations from the agency perspective over the years. I would also say that we're hearing from patients that the need is urgent now. Thank you for your question.

DR. BUTLER: Dr. Peterson, you have a related question?

DR. PETERSON: Yes. Just back on this issue, I'm struck by that you hear from the audience incredibly compelling stories about an acute and actually nearly miraculous effect of the drug, huge effects on their lives over a short period of time. You show in your non-randomized data, again, large effects in a small number of patients, and yet when we do the first randomized trial, you show no effects that are measurable.

MS. McCARTHY: That's right.

DR. PETERSON: If the reasoning is just time, you could study similar numbers of patients, and if the results we are seeing hold out, you

should see it. You should have seen it within 3 months, but if we assume that the time factor was the issue, you could not necessarily need to do more extensive rule out of very small changes. You're expecting to see large changes, and maybe it's a time factor, but that should be easily studied in a reasonably powered study, even for this disease.

MS. McCARTHY: Maybe you can pull up slide 5 that you're showing there so that we can show the full answer from the crossover period. I know that the agent said this was a question. Yes, that slide; please pull up the slide.

In the 3-month treatment period of the crossover trial, we really did not see any change from prescreening values on 6-minute walk test. We don't see that. The placebo effect as it were does not exceed any of the prescreening values, and again, we didn't see any treatment effect on any of the other functional endpoints either. So it is pretty clear to us that 3 months was insufficient to see changes across this cohort.

We recognize that some patients were reporting improvements, but it obviously wasn't significant overall, and there is variability in genetic mitochondrial diseases, and we are always going to be dealing with small sample sizes. So I think it's hard to suggest that in a short trial that isn't adequately powered, we might be able to see this. I think that's some of the discussion we've been having with the FDA over the years about how to actually power trial.

In addition, we had enrolled all of the eligible patients in the United States at the time in this trial and, again, other studies ongoing in Europe. So I think that there were just practicality issues and feasibility issues in terms of why we couldn't conduct another trial at that time. The decision we made was to try to control the open-label data in the best way we thought possible with the natural history control study. From our perspective, the time when we really started to see benefit was after about 6 to 9 months on therapy.

DR. PETERSON: But again, that was with a very small number of patients. If you studied a very small number of patients for 6 to 9 months, you should be able to see significant effects that you saw within the uncontrolled trial in a controlled trial, now taking care of the biases and and potential challenges of that uncontrolled study.

MS. McCARTHY: Sure. It was 24 patients because each served as their own control with a crossover design, which I don't think I would repeat given the challenges with that. So that was 24 patients, and we did propose that as a randomized clinical trial design to the department in 2021, early 2022, and the conclusion was that that would be underpowered.

DR. BUTLER: Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor, Inova, and two quick questions. One is, the clinically meaningful change in 6-minute walk test varies by disease state, so the FDA and investigators have encouraged anchoring analyses in clinical trials;

that is to put the patient global impression to anchor what the change would mean. Do we know what the clinically meaningful difference in 6-minute walk test is in Barth syndrome?

MS. McCARTHY: We haven't anchored it specifically in patient or clinician global impression scales, although you do see the movement of those together, but we did have written feedback from the Division of Neurology, the Division of Rare Disease and Medical Genetics, and the related mitochondrial disease of primary mitochondrial neuropathy, that a clinically meaningful effect would be 25 meters. That's how we powered our phase 3 development efforts in primary mitochondrial neuropathy.

DR. O'CONNOR: Okay. And just to follow up on the question that we gave the FDA, what is your explanation for the differences in the behavior of the placebo patients in the two sequences?

MS. McCARTHY: Can you pull that slide up one more time? The biggest difference we see is actually is the change between screening and

baseline, which we are attributing to fatigue based on discussions with experts because of rapid travel for those successive assessments. We're getting to speculation at this point. What is notable is that you actually don't see that sort of drop again post-recovery in the elamipretide-treated patients going over. I don't know. I mean, there are whiffs of the carryover effect. It wasn't statistically significant, but what you see there might suggest there was some carryover effect from the patients randomized to elamipretide.

DR. BUTLER: Thank you.

Dr. Johnson?

DR. JOHNSON: Jon Johnson from Mayo Clinic. My initial question was to Dr. Chatfield, trying to clarify a couple of things about some of the cases. Dr. Halnon from UCLA actually just took care of that. My question was about the explants, and that one patient needed a transplant, and whether or not you were able to see anything, but it sounds like there was something more going on there.

For any of the other patients, do we have

any tissue, human tissue, [indiscernible - 6:53:11] tissue; like for instance, in Baby Declan who had the VAD taken out, when that VAD was removed, where we have myocardium that's been treated with elamipretide to see if there's anything different?

MS. McCARTHY: Not in the Barth patients, but Dr. Chatfield has actually done extensive work with explanted human heart tissue, including in pediatrics.

Dr. Chatfield?

DR. CHATFIELD: Thank you. Kathryn Chatfield. To answer your question, Dr. Johnson, we have studied explanted tissue from patients with Barth syndrome, and we've published on that, and it shows the metabolic deficiency that they have, but we have not had one of those that was treated with elamipretide. We have separately studied explants from patients who were transplanted at the University of Colorado, children and adults that were treated ex vivo subsequent to explant with elamipretide, and we showed in a JACC BTS paper that just a short-term treatment with the drug can

actually improve respiration.

DR. BUTLER: Dr. LePichon?

DR. LePICHON: Thank you. J.B. LePichon. This question is actually for Dr. Vernon.

Dr. Vernon, you know every one of these patients since you've treated them all. I can't help but notice that about 20 percent of them, on each leg of the trial, have dropped out for one reason or another. We've talked a lot about that local site reaction, and it really makes me wonder, for a drug that supposedly changes their life so much, can you explain a little bit more about why those patients dropped out? And maybe even if you can say a couple of words about the couple of patients who dropped out and then decided they wanted to come back in. Help us understand the significance of this injection site reaction and how it impacted the children's lives --

MS. McCARTHY: Yes. Dr. Vernon?

DR. LePICHON: -- as it relates to their improvements.

MS. McCARTHY: Yes. I note two of the

dropouts were after the crossover, so not quite on the long-term therapy.

Dr. Vernon?

DR. VERNON: So as you mentioned, everybody is near and dear to my heart, and the most important thing to me is that they're safe; everything else, bar none. The two young men who had injection site reactions, one of them, we had extensive discussions because he lived alone and was scared; what if his reactions got worse? And he was just very, very, very nervous, and I did not think that that kind of emotional stress was worth pushing. But after he went off and, unfortunately, kind of stepped out of the trial, he wants to come back, and just based on the study itself, we can't do it. That's one experience.

The other experience is also a patient who lived at a distance from me who was experiencing injection site reactions, that I felt unsafe managing from a distance. Again, there weren't any other signs of anaphylaxis, difficulty breathing, anything like that, but because it's an

investigational drug, to me, safety is just the most important thing. And because he wasn't near me to keep an eye on these things and manage these things, together we made the decision to discontinue, which was a heartbreak, and he also would like to re enter.

Did that answer your question?

DR. LePICHON: Yes. There were a few more patients who chose either not to continue or to pull out. Do you have any comment about those?

DR. VERNON: No, other than that they were no different from the rest of the patients who entered the clinical trial. There wasn't anything I could think of that differentiated them in terms of their baseline values or their clinical presentations.

DR. LePICHON: Thank you, Dr. Vernon.

DR. VERNON: Sure.

DR. LePICHON: If there is a second, I had a couple of more questions; if not, I can skip them.

DR. BUTLER: Yes.

DR. LePICHON: Just one more.

MS. McCARTHY: Go ahead.

DR. LePICHON: One more question, then. I'd like to give the sponsor a chance to respond to some of the FDA's criticism about the echocardiogram work that was done, specifically to address the 2D and 3D echocardiograms that were done in the natural history cohort and how that affects the results.

MS. McCARTHY: Thank you. I know there were a couple other comments that were left over from before, too. In terms of the natural history echocardiogram post hoc analysis, that was conducted at the request of the Division of Rare Disease and Medical Genetics, starting back in 2020. So that was a post hoc that we did at FDA's request. We took what data was available in the natural history cohort for patients who had serial echocardiograms.

Again, the natural history study was designed with a lot of rigor to match on the basis of 6-minute walk test, and age, and height, so it wasn't really designed, at first, to look at the

echo results; that was, again, something we went back and did. So again, we have limited data and limited ability to match the characteristics of those echos. You noticed that we didn't put much about it in our briefing book or our slides. We view it as supportive, but we recognize the limitations of the analysis.

DR. BUTLER: Thank you.

Dr. Tucker?

DR. TUCKER: Yes. Thank you. Carole Tucker from University of Texas Medical Branch. Just a few quick questions for the sponsor concerning some of the outcomes and what I'm perceiving as a troublesome 6-minute walk test distance.

I've noticed in two places, it was mentioned that an impaired 6-minute walk test was actually an inclusion criteria. Were there any patients -- and I'm assuming maybe no -- that couldn't be included because of that? Then the second part really is, based on the really compelling patient stories, caregiver stories, we're hearing a lot about fatigue and weight gain as other really meaningful

outcomes and quality of life. And even though it seems quality of life was measured as your patient and caregiver change, fatigue was one single outcome measure.

Could you maybe talk a little bit more about how in a future study -- or what outcomes may be relevant, and what is the impact of that 6-minute walk test as your primary outcome? Would you go there again?

MS. McCARTHY: Well, the 6-minute walk test has rich regulatory precedent. It was deemed appropriate in the setting of Barth syndrome, and it was recommended to us by the FDA. So as we said, in 2016 designing this trial, it was the right outcome, and it is better in larger sample sizes because you can overcome the variability that you see.

Notably, in Barth syndrome and during that crossover, we actually didn't see that much variability with pre-assessment assessments if we look at screening, so there wasn't actually much change until longer term therapy. But no, we've

since discussed the utility of something more like CPET, but that would have excluded a number of patients who can't really complete that assessment, and at the time it didn't have regulatory precedent.

Fatigue, we tracked; we measured. You actually see a more temperate response on fatigue. It it improved in the open-label extension, but maybe not as much as some of the functional assessments. I think we think it's remarkable that fatigue improved despite the functional improvements. It also wasn't collected according to the instrument as it was designed in the open-label extension. It was designed to be collected daily during the trial, and it was really only at assessments in the open-label extension. So it's one of the reasons why we prioritize looking at the Patient Global Impression, which is more designed to be looked at, at a given timepoint.

Does that answer your question?

(No audible response.)

MS. McCARTHY: Thank you.

DR. BUTLER: I have a couple of quick questions. When we heard this morning from the sponsor side some case reports from the Expanded Access Program, and then obviously we heard in the open public hearing session as well, they were pretty remarkable. Can you just give us a sense of the total universe of the Expanded Access Program and what do these cases represent? Are they 10 percent, 19 percent? What's the total experience like?

MS. McCARTHY: Overall -- and forgive me if my numbers aren't spot-on, but they're going to be close -- we've exposed around 22 subjects with expanded access therapy. Seven of those are going to be subjects who rolled out of our TAZPOWER Extension trial. So there are a number of cases with patients exposed on expanded access therapy. The case studies we've profiled are the ones where we have published reports.

One of the limiting aspects of expanded access is that you don't collect data

systematically as a sponsor, so if you can get reports or letters in from cardiologists, which is some of what we profiled to you, that's when we can really recapitulate. What we do know more broadly in that expanded access program is that I think there've been 10 kids under the age of 12 exposed to elamipretide, and we haven't seen anything untoward from a safety perspective. And that's really why we profile those cases, because we recognize the utility, the need, in younger children. We don't really have efficacy data per se, but we do have limited safety experience.

DR. BUTLER: Great. Thank you.

The other thing that we heard is that there are a lot of clinical consequences of this disease, whether it's cardiovascular, GI, nutrition, a whole bunch of hospitalizations, infections, et cetera, and even as exploratory analysis; we just saw data on functional capacity and symptoms. Do you have any cumulative idea on the clinical outcomes in these extension, long-term studies, what happened to the patients and the number of events, or

hospitalizations, or something?

MS. McCARTHY: Yes. I'd like to ask Dr. Vernon to come up. I will note that we studied kids during adolescence, and unlike what we would have expected during puberty, we actually saw improvement instead of decline. But Dr. Vernon's in touch with these patients longer term.

DR. VERNON: I'm going to do my best to recall. We talked on the phone quarterly, now at this point, and our phone conversations -- I hope this illustrates how well people are doing -- at this point are, "Hey, I'm calling for your quarterly safety data," and the responses to me are, "Nope, haven't been hospitalized, no change in medicine, doing fine. Let's go through our EQ-5D, I want to get on with my day," which I hope speaks to the fact that we are seeing really very limited adverse events at this point. When I think back to the number of serious hospitalizations throughout the open-label extension, I can recall one due to infection. I hope that answered your question.

DR. BUTLER: Thank you.

Then your inclusion criteria was age greater than 12, but then your exclusion criteria were kids who might be going through rapid puberty or something to that effect. Why age 12? And then if this drug is approved, will it be limited to kids greater than 12? Why not give it to younger kids?

MS. McCARTHY: Well, that's a bit of a question that we need some guidance on. The reason for age greater than 12 was feasibility. You want to get kids who can do the assessments. Frankly, many children, even some of the 12 year olds, didn't qualify for the weight-based cutoffs that we were looking at from a safety perspective, and you want to ensure that they can do the assistance, and you want to limit heterogeneity, particularly when you're dealing with such small sample sizes. So that is why we picked age 12 and up at the time. I don't know if we actually excluded anyone for going through puberty. We did not, so it didn't translate into an issue for us

I'm sorry. I missed the second part of the question.

DR. BUTLER: But if the indication is granted, will it be limited to greater than 12?

MS. McCARTHY: I think that's a question for the FDA. Our suggestion was to look at weight-based dosing based on where we have weight-based experience in patients with Barth syndrome. That said, this is a genetic mitochondrial disease which you've heard affects children in utero and throughout their lives, and elamipretide is targeting cardiolipin, which is the root cause of the disease. We certainly don't see safety issues in younger kids. We certainly see the utility. We don't expect there would be a difference, based on age, in terms of potential efficacy or benefit. In fact, earlier, most clinicians would say it would be better before we have some of the pathological remodeling of the muscle and heart systems.

That said, our dosing right now is weight-based, based on modeling of PK. So at a minimum, we've committed, if approved, that we would do a postmarketing PK study in children to inform better

dosing. We don't know whether we're optimizing the pediatric dose.

DR. BUTLER: Thank you.

Dr. Shaw?

DR. SHAW: Yes. Thank you. Pamela Shaw. I think my question got a little separated, from time, from Dr. Peterson's. This is one more discussion about feasibility just because of how difficult these data have been to interpret, feasibility of doing additional data, because I'm hearing some mixed signals in the sense that I also heard at 36 weeks, you provided evidence for the long-term follow-up of 100-meter changes in that 6-minute walk, significant differences with 8 people.

So I first want to recognize, absolutely, it is so challenging to do clinical trials in a rare disease. I also want to recognize the incredible work of the Barth Foundation, which is a shining light in these situations, where there's a real unifying source amongst families and other supporters to create this connection between

patients and between patients and the scientists.

You enrolled, in less than 3 months, 15 people, and that was a tremendous success and an exciting one. So when I hear great connections with the patients and the foundation, I hear you were able to mobilize 15 patients in 3 months, huge changes in maybe 6 months of therapy, and a crossover design which allows you to enroll half the people and get twice as much. In your own crossover trial, I read that all of the randomized subjects finished, so I'm not hearing the difficulties.

So when you say, in your concluding statements this morning, you think it would take years to do a randomized trial, I do need more help understanding that because repeating a design that's been suggested by a few people is very similar to the one that took you 3 months to recruit, but maybe letting the periods last 6 months, what's the fault to my logic? Why is that not feasible?

MS. McCARTHY: First and foremost, there are

more people in the room today than I think are living with Barth syndrome in the United States, so it's an incredibly small patient population. We can't enroll all patients because you introduce variability if you're trying to get to an answer. Some of them are not suitable for treatment, some of them may not be able to travel, some people don't like to participate in clinical research.

So when we did the study in 2017, we enrolled all the patients that -- the Barth Syndrome Foundation and Dr. Vernon -- would be eligible or willing to participate in this trial. It was broad canvassing. It did enroll quickly, but that was because we worked on it for 2 years ahead of time, and the patient community was aware and ready, and we thought we had exhausted all available patients at that point.

Now, time has gone by, and maybe other patients have aged in, but also we suggested a lot of different trial designs along the way, and really couldn't get to alignment with the agency on any of those. So it's been a long time period, and

we think we have data that is interpretable now. We think that the drug is improving the lives of patients now, and we think the need is urgent and unmet now.

DR. SHAW: Thank you for that response, and just a clarifying question. This morning, Dr. Ellenberg asked you, there were a bunch of patients in the natural history study that seemed eligible, why weren't they enrolled? And you actually said that it's because you've enrolled so quickly that you completed enrollments; that you weren't able to enroll all the patients that were eligible. So I just want to clarify, because you're contradicting that in your current response.

MS. McCARTHY: No. I appreciate Dr. Vernon shared that. I think really what she said was that the patients who didn't enroll were enrolled in a competing study at the time. So again, the trial did enroll relatively quickly. I think it was between July and February of the succeeding year in terms of completion of enrollment, but that was largely due to a lot of canvassing ahead of time of

the patient community.

Again, it's not like we didn't suggest additional clinical investigation from that point forward. We did this natural history control study, which was very rigorously conducted, to try to improve the interpretability for the patients that we had. We proposed randomized withdrawal with designs and we proposed additional trials, but I think there were real concerns about how to power another trial in this disease. I don't think we'd do another crossover either, quite frankly.

DR. SHAW: And maybe a final question is, given the success of that crossover trial that everyone finished, why wouldn't you do another crossover trial?

MS. McCARTHY: I think some of the questions that were just raised revealed some of our concern that there was a carryover effect, and it's really kind of hard to quantify that going into a study.

DR. SHAW: Okay. Thank you.

DR. BUTLER: Dr. Jonsson-Funk?

DR. JONSSON-FUNK: Thank you. I have two

questions about analytic issues that were relevant to the natural history study. The first is, I wonder if there was any consideration given to the use of sampling weights to account for potential differences between the total population of those in the 79 individuals who could have from the registry been included versus the subset who met all of the requirements.

Then my second question has to do with why you chose to use propensity scores, given the limited N here for building a propensity score model with just 8 individuals, really, on your outcome side of your propensity score model.

MS. McCARTHY: Yes. While Dr. Wittes is coming to the microphone, could we also pull up the observed values slides that we've prepared for sharing because we have also looked at the natural history data relative to observed values.

Janet?

DR. WITTES: Yes. I'm a little confused about your referring to the 79. We really felt it was important to have the controls to be the people

who would have been eligible for the study. So, to me, those 79, or most of those, would not have been eligible for treatment. So it's really the 24 who would have been eligible.

The next question is why propensity scores? There were some strong feelings among some of the people that that was the way to go, even though everybody knew that it's very hard to do analyses for tiny sample sizes. So I don't have a good answer for that, why that was the decision, but it came out of a consensus of a lot of discussion among different people who had somewhat different opinions.

MS. McCARTHY: If we could just take a quick look at the observed values because I think that might help with this question as well. It's not that slide but next slide maybe. Yes, that would be helpful.

Apologies to the formatting of this, but based on some of the questions, this is data that has been shared with the FDA, although recently in response to the late cycle review meeting. This is

showing change from screening values to give ourselves that haircut from screening based on only actual data for both the treated set and the natural history cohort. We don't have observed values for all the timepoints, but for the week 100 assessment, which was conducted post hoc at the request of the FDA, 15 of the natural history subjects do have observed values. So we can see a very large treatment effect, again, even benchmarked to screening.

If you can show from baseline as well, next slide. Similarly, that effect holds when we look at it from baseline, looking at only actual values, not imputed. You can put the slide up. Sorry. I hope that's helpful for the question.

DR. JONSSON-FUNK: Thank you.

DR. BUTLER: So I'm cognizant that we are running significantly behind. I'm also concerned that several members have flights. I'm going to give the last question to Dr. Ellenberg. I have many names still here, so if we can just relook at the room, and those questions that have either

partially been answered or answered, then I won't go through the list. If you have some other really pointed questions, then please let us know again.

Dr. Ellenberg?

DR. ELLENBERG: Thank you. Could you put up the sponsor's slide 41? When I look at very small sample sizes, I'm interested in looking at the individual patients. Means and standard deviations are hard for me to interpret when we're talking about 8 people. I want to see exactly what happened. And this was a slide, an example of something. I have no idea who's in this slide? There's age at the bottom and different timepoints. Does each point -- what's represented in this slide?

MS. McCARTHY: This is Dr. Vernon's data. This isn't the sponsor's data. This is from her natural history study conducted well before Stealth started clinical trials in the setting of Barth syndrome. I believe -- correct me if I'm wrong, Dr. Vernon -- that each peak represents a patient, and it's shifted over by one point. But again,

this is data that predates our investigation and our clinical development efforts.

DR. ELLENBERG: Okay. So there's no follow-up. It's one point. Are people in there more than once?

MS. McCARTHY: So the blue line shifts 2 years later to the green line with the peaks superimposed; so where you see that arrow, that peak is patient at 2014, and in the green, it's that same patient at 2016.

DR. ELLENBERG: Okay. It's hard for me to assess the variability. This looks very variable --

MS. McCARTHY: Dr. Vernon?

DR. ELLENBERG: -- but I don't --

DR. KISHNANI: Yes. If I could also add here -- because I know we're running out of time, and this was exactly my question -- the need for a really good natural history study, we know this is so important; that showing those data or doing those now, prospectively, would significantly help in the situation.

DR. VERNON: This paper was published -- I don't think this was our Genetics in Medicine paper. Oh. This is Journal of Rare Diseases in 2019, the Orphanet Journal. So I apologize for the confusion in my rush in going through describing this. The best way to think about this is we were able to look at the same cohort of 16 patients, the same people at the meeting in 2014 and in a meeting in 2016. Each angle of the line chart, if you can imagine a dot there, that represents a single patient. If you can imagine that dot on the blue line, moving over to the dot on the green line, that is the same patient. So this isn't variability within a patient. These are individual patients, how each of them performed, and moved over 2 years.

I hope I'm explaining this. I'm waving my hands a lot, but I hope I'm explaining this properly. The 6-minute walk test is on the Y-axis and age is on the X-axis, so you can see they're 2 years older. So across the population, the average across the population didn't change, but

also within individual patients, their 6-minute walk test distance didn't change.

Does that help? Hopefully.

DR. ELLENBERG: Yes.

DR. VERNON: Okay.

DR. ELLENBERG: The other question, we heard 4 case studies that were very impressive all in infants, so I'm wondering whether you are studying this in infants. If these infants have such an incredible response, why --

MS. McCARTHY: These infants are born at all different hospitals. We don't know when. We don't know when that will happen. They're in acute cardiac distress, and it's pure serendipity that they find their way to us through expanded access. We don't know a way to do a prospective trial in infants, quite frankly, in a disease this rare.

DR. ELLENBERG: Right. So no plans to do that. Okay.

MS. McCARTHY: There was a question before the break about the mouse model of Barth syndrome. Just as a note, in the published paper, there was

no sign of cardiac dysfunction in that TAZKD mouse model. There were signs of cardiac mitochondrial dysfunction, which were ameliorated with elamipretide. That paper is published in Nature. It's Russo.

DR. BUTLER: We had some leftover questions for the FDA as well. Is there any question that anyone wants to ask the FDA?

(No response.)

DR. BUTLER: Any final question to the sponsor?

DR. KISHNANI: I have a final question for the sponsor. I know of one biomarker, which was the MLCL to CL ratio, but we also know, and we heard from the testimony, about methylglutaconic acid. We see other such findings on urine organic acids, also lactic acidosis, et cetera. Was that monitored? Was any difference noted?

MS. McCARTHY: Dr. Vernon? It was monitored, I believe.

Dr. Vernon?

DR. VERNON: As part of my natural history,

I've spent many, many years looking at 3-methylglutaconic acid, and it has no correlation to clinical status at all. Some of my babies in the worst failure have normal 3-MGC, and some of my guys who are doing quite well have elevated 3-MGC, and I just can't predict it. It's a nice biomarker that mitochondrial disease is there, but a pretty poor clinical status biomarker.

DR. KISHNANI: If I could ask a follow-up question, though; if there's an improvement in mitochondrial function in someone who had an elevation, would you expect to see a normalization, and was that looked at?

DR. VERNON: Would I expect to see a normalization of 3-methylglutaconic acid if a patient were doing better? I honestly don't know because it's just not what I see in the clinic. It doesn't correlate with Barth syndrome in real life, so I'm not sure what I would do with that in a clinical trial.

DR. BUTLER: Thank you.

Dr. LePichon?

DR. LePICHON: This is a yes/no question, I swear. In the material you distributed to us, I believe that you mentioned that in the last year, in the expanded access study, you recruited 40 patients in one year. Is that correct?

MS. McCARTHY: Oh my gosh, no. That's overall number of requests that we've received since we've been developing elamipretide for the treatment of Barth syndrome.

DR. LePICHON: So you received 40 requests in one year?

MS. McCARTHY: No, no, no. Since two thousand -- I don't know -- 17.

DR. LePICHON: Gotcha.

MS. McCARTHY: Yeah, yeah, yeah. In the past year, and you've seen actually most of the infants who've requested, and you've seen most of the people who've requested, expanded access in the last year in the room today or heard from them.

DR. LePICHON: Gotcha. Thank you.

MS. McCARTHY: Yes.

DR. BUTLER: Very well. Thank you very much

for this extensive discussion. I'm sure there will be a lot of things that will come up in the committee deliberations as well.

We will now proceed with the charge to the committee from Dr. Joffe.

Charge to the Committee - Hylton Joffe

DR. JOFFE: Thanks very much.

As the committee's about to start its discussions, deliberations, vote, I just want to remind you all what we're asking for. We're asking you to discuss whether the evidence that you've heard today, that the company's provided on elamipretide, supports a conclusion that elamipretide is effective. And again, it's considering results from SPIBA-201, Part 2, SPIBA-001, and the applicant's other proposed supportive data.

Then after completing the three discussion questions, we're asking you to vote on the following, which is, based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome?

There are four important considerations I'd like you all to keep in mind as you do these deliberations. First, remember your role is to consider the assessments, the conclusions, the perspectives from both the applicant and the FDA review team, and then provide us with your independent expert advice and recommendations.

Second, I want you to put safety aside. I heard some bits of trickles of safety coming in during the day. Put that aside. What we're really asking you to do is focus your discussion on effectiveness; again, whether the evidence you've heard convinces you that elamipretide is effective for the treatment of Barth syndrome. We're not asking you to do a benefit-risk assessment or weigh benefits against risks. It's really an effectiveness question.

Third, I want to encourage robust, thorough discussion of the three discussion questions. Then lastly, when you vote, remember that your rationale is more important than the vote itself, so please provide detailed rationale for your vote, and with

that, I'll turn it back to the chair.

Questions to the Committee and Discussion

DR. BUTLER: Thank you very much.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning the wording.

Question 1, discuss whether SPIBA-201, Part 2 demonstrates that elamipretide is effective for the treatment of Barth syndrome. Include in your discussion the interpretability of the single-arm, open-label study design and findings on 6-minute walk test; other functional outcomes; echocardiography; patient-reported outcomes; and cardiolipin ratios.

Are there any questions about the wording of this discussion point?

MS. SHUMAN: Hi. Yes. This is Devin Shuman. I raised my hand and have a question. For the purpose of these questions, I just want to clarify, "is effective for treatment," are we supposed to differentiate in our head between full approval, accelerated approval, or just overall? Sorry. This is my first committee.

DR. JOFFE: This is Hylton Joffe from the FDA. So, of course, full approval and accelerated approval are two different pathways for approval. Full approval is something that's based on endpoints in terms of how a patient feels, functions, or survives, sort of like how they perform on a 6-minute walk test, for example.

Accelerated approval is usually based on a surrogate endpoint that is reasonably likely to predict clinical benefits, so it could be echo data, for example. But in that case, you've got to still have substantial evidence of effectiveness on that surrogate endpoint, and you have to believe

that that surrogate endpoint is reasonably likely to predict a clinical benefit.

So as you walk through all these issues and think about the evidence, you may at the end decide that there's evidence for echo -- I'm just making this up -- and then you would tell that to us in the feedback you have and how you vote, and then it would be back on us to then take that back and figure out what the right pathway is and things like that.

Does that answer your question?

(Ms. Shuman gestures yes.)

DR. SOSLOW: Sorry. This is kind of a dumb question, but there are a lot of cardiologists here, and it seems like a cardiac panel, and a lot of these outcome measures can be cardiac. Are we supposed to look at this from that bent? Like did the 6-minute walk test improve because the cardiac function improved or because their heart improved, or are we supposed to look at this as if we're neurologists, and did they have less fatigue and better muscle strength? Because I'm not a

neurologist, I just wanted to clarify that.

DR. JOFFE: Good question. And we do have a makeup on the committee where we have neurologists, for example, and cardiologists. So I think weigh in based on the expertise you have on these questions. If you feel you don't have expertise about a specific element, we don't expect you to opine on that.

DR. STEIN: Perhaps I could just add one clarification. We're not really asking you to interpret the nature or the mechanism of the change. We're really asking you to interpret the data as you've seen it in the presentations. So you may postulate whether it's through a mechanism that you're more familiar with, or a different mechanism, but really to focus on the results of the trial.

DR. BUTLER: Dr. Johnson, you have a comment?

(Dr. Johnson gestures no.)

DR. BUTLER: Great.

If there are no further questions or

comments concerning the wording of the question, we will open it up for discussion amongst the committee members.

DR. GERHARD: Sorry. I had a question from online. I raised my hand. Toby Gerhard, Rutgers, and just a quick question. In the interest of time, does it make sense to separate question 1 and question 2, given there will be so much overlap in the discussion?

DR. JOFFE: So that's the current structure, and I think there are little differences that we can discuss. So 201, Part 1 is a randomized part that did not show improvement, and the discussion is whether Part 2 obviates some of the concerns that might have come with Part 1, and I think it's a little bit of a distinct question; then there are the questions that are pertinent only to natural history per se and how reliable, or not, the natural history data are.

So I think eventually the whole discussion will merge, but at least in the beginning, if you can just focus on Part 2, that will be very

helpful.

DR. GERHARD: Perfectly fair. Thank you.

DR. BUTLER: Dr. Ellenberg?

DR. ELLENBERG: About 25 years ago, I was working in AIDS research, an area where there was not a dearth of patients but very strong feelings against doing uncontrolled studies, especially with placebo controls, and a group of us, a large group of statisticians, ended up writing a paper that was published in the New England Journal of Medicine that listed a set of criteria for when you could or should do an uncontrolled study that might produce valid results, and I think it might be useful to talk about those criteria.

One, there was no known effective therapies. Okay, we have that. Secondly, there is enough experience to expect a uniformly poor outcome of people who are untreated, so we can think about that. The second is the effect is expected to be large enough, to be persuasive, without the use of control. They're not expected to be safety issues that could possibly outweigh the benefits, and that

there is preclinical evidence that provides strong biological plausibility for the effect.

Now, I am not a cardiologist, or a nephrologist, or any of the other clinical areas that are relevant, so I can't make that judgment about whether these differences that we saw are so great as to be persuasive without a control, or whether the experience, the natural history experience, is so uniformly poor that you wouldn't expect to see that kind of improvement. My sense from looking at the data is there's a lot of variability in the natural history control group, but I need to hear from the people with the medical expertise on these issues.

DR. BUTLER: Any responses from clinicians?

DR. SOSLOW: I can take that from an echo standpoint. I spend all of my time reading imaging studies. I was disappointed by the both 2D and 3D EFs in there. I was disappointed in stroke volume as an outcome measure and really didn't feel that the echo data convinced me. And I also felt a little disappointed that the natural history study,

I didn't feel like I understood what the natural history was in these patients, especially from a heart standpoint; and that's coming from someone who is running a natural history study right now in a rare disease because of that problem in order to try to get these answers. So that's my perspective from an echo standpoint.

DR. KISHNANI: I could also add here, I've been part of open-label studies leading to drug approval, but the natural history competitors are done in a very systematic way, and I must say that in this situation, the natural history study has just left me with more questions than answers. It's not systematic. I can't really tell how to compare these patients to the natural history. The data points are not right there, so that to me has been a big challenge; including even looking at the MLCL, you don't see those data in the natural history. So once again, it makes it hard to draw some conclusions here.

DR. O'CONNOR: Chris O'Connor.

Susan, thank you for bringing that up.

That's an important paper; that I didn't remember any of that criteria, so thank you. I think a lot of those criteria were met. When you talk about a 96-meter increase in 6-minute walk test, that is very large. Their estimand was 25, so we're talking 4X about what their estimand was. Now, obviously we don't have a control in this first question, so we want to see large. But if that came in at 25 or 35, which is typically what one could get approval on in a well-conducted, controlled clinical trial, then there would be a lot of doubt, but 96 is large.

DR. KISHNANI: Could I ask a question there? I thought I saw in the natural history, there was a change in that direction for one of the patients. That's what really got me confused, unless I saw that incorrectly.

DR. BUTLER: Yes. So you're talking about the individual patient plots, and that one patient was significantly higher, and that could have raised the mean. Yes, sure, so that point well taken.

DR. KISHNANI: The natural history study, I thought were in that same realm of improvement as in the treated group, which as a clinician, I agree that anything above 30 meters, we consider very clinically meaningful. But when you have so much of a spread, even in the natural history untreated group, it just got me a bit concerned.

DR. BUTLER: Dr. Johnson?

DR. JOHNSON: Thank you. If I can just add to Dr. O'Connor's comment, I agree with you that that change is significant. For Dr. Soslow's mention about the echo data, we're so fraught with error when we're measuring a lot of these different things on an echo, and many of our studies that we've done for a long time, really, we had to be really cautious about this. And it's really hard to get anything published in echo journals for that reason because we have to be so specific about it. So it would be very hard for me to vouch for this particular indication purely based on the echo data, and I agree with you, Jon, about that.

That being said, I think when I came in

here, I was a little bit more worried about the 6-minute walk data based on some of the concerns that were raised by the FDA reviewers, which I think was very appropriate. I do think a lot of that's been fairly well addressed by the sponsor and by the the audience as well. So I have less concern about that than I did when I came in.

DR. BUTLER: Can I ask a question to our statistical experts on the panel? We heard two perspectives on both issues. One was the imputation, and the other issue was propensity matching and whether the small number of patients, 2 or 3 variables for propensity matching, does that really take care of all the confounding as much? What does the panel's statistical expertise have to say about their perspective on imputation and propensity matching, and how satisfied should or should we not be with the data that we saw? We had a different perspective from sponsor and FDA on that.

DR. SHAW: Pamela Shaw, biostatistician. I'm at Kaiser Permanente. This is a difficult

problem. There are very few patients, so I'll start with the propensity score. The idea of propensity, you're going to try to equally weight the two groups to be representative of the variables you're trying to balance. They only balanced three things. I think it was age, height, and maybe the 6-minute walk score.

They chose those out of feasibility because they couldn't -- what you want to do is choose all the variables that might make people joining the clinical trial different than people in natural history. I think with so few variables, it was the practical limitation that drove them there. If they had had a huge patient cohort, they would have thrown in tons of variables.

So I think it is a very limited propensity score, and all they're doing is balancing baseline characteristics. What they're not balancing is, we heard, called informative presence bias. We don't know why those measurements were taken. Why did they show up at that time in the natural history study? Was it because they were not feeling well?

There are no variables that we would even know what to put into the propensity score.

So I find it's a very challenging, limiting situation to think that three variables could somehow undo that kind of selection bias, so I have my doubts. I also think there are many papers talking about the technical limitations of fitting what was likely some kind of logistic regression, where you have such few number of points, 8 points or however many, and it's a very unstable and a good chance of overfitting. So I have my doubts of a propensity score that probably was unable to do its job. I would have concerns about residual confounding.

With regards to the imputation, my little bit of agitation in the morning, I get a little excited. Statisticians get excited when they talk about numbers, so please, I have no ill-will towards those doing imputations, but I am upset by how that technology was done because I find that, statistically, how it was done, two things bothered me about it.

One is, we saw how variable the data are, and they had to interpolate points to try to find the measurement time they wanted, something like 64 and 76 weeks. That's fine. That's a normal procedure for data to have variability. But the normal way you then do your analysis to look at a p-value is to represent the uncertainty of your data. The full uncertainty of the data can only be captured by a multiple imputation technique that would put all of that uncertainty about the lines you were connecting, and that wasn't done. So I'm very concerned about any p-value that is totally non-representing the actual uncertainty of the results.

The second thing was the way the imputation was done. You replaced an observed value with a prediction as an outcome, and then did nothing in the analysis to account for the fact that that wasn't the data point, that that didn't have the distribution of a true data point, but it was a prediction, and I have concerns over bias. So I felt like there were a lot of methodological

concerns in how the imputation was done, and maybe on top of it, the small samples, that's even small compared to the other problems I saw.

DR. BUTLER: Any additional comments?

DR. ELLENBERG: I agree with Dr. Shaw on all her points -- this is Susan Ellenberg -- but again, I would say that with so few patients, I'm not sure I would even attempt to try and do a propensity analysis, or regression analysis, or anything. I would want to look at the individual patients. We saw a few spaghetti plots that Dr. Bai presented, and I would have needed to see much more of that to have felt like I had some understanding of the data.

DR. ALEXANDER: Caleb Alexander. I'm not so troubled by the echo results. I don't think I heard the sponsor say that they're proposing that this is a reasonably likely surrogate in a regulatory sense, and I guess from my clinical training, I think we've all seen plenty of cases where the echo results didn't really match the patient. So I don't have a hard time setting aside

the echo results or not; or at least let me put it this way. I wouldn't want to overweight them in swaying my belief as to whether or not this product works or not.

I think it's really hard to interpret the results of the open-label extension study for the reasons that we've discussed, the concern about placebo effects and the concerns that you can use state-of-the-art methods to match till the cows come home, but that doesn't overcome the fact that you have an effort-dependent outcome, which is I think, really, the elephant in the room.

Then I just wanted to say one comment that two other panelists have talked about, trying to reconcile the striking results that one heard from several open public hearing participants with the absence of any effect in the randomized trial. In fact, earlier I asked why the sponsor felt that this product had not succeeded in prior trials, and the answer seems to be it hasn't been studied for long enough.

The FDA has a slide 48. We don't have to

put it up, but you can find it. And essentially it shows that by week 12 in the open label, the participants have achieved 50 to 65 percent of the total gains, if I'm reading it correctly. So it's just striking to me that you have a product that if we believe it works, there's no separation of participants at week, I don't know, 28 or something, and then somehow between week 28 when you stop blinding, and week 40, which is 12 weeks into the open label, suddenly the participants have obtained 50 to 65 percent of the benefit of the product with respect to the outcomes being measured.

I just can't get my head around that, and I guess that also makes me concerned that the effects that we see are not necessarily from the product itself but rather from the potential for things like the open-label unblinded nature of the assessments as they were being performed. Thank you.

DR. BUTLER: Thank you.

Yes. I was thinking about the echo results

myself, and I think that I am personally not concerned about not having the same echo results in other adjacent diseases because those diseases have very different pathophysiology. So if you have regular heart failure, there are so many things going on other than the mitochondrial effect that I don't think you can extrapolate the data from other diseases to this disease, where the primary problem is the mitochondria, so that doesn't bother me.

But I do have a question, and maybe Dr. Soslow again can answer. There are other diseases with the smaller ventricular size, non-[indiscernible - 7:46:19] hypertrophic cardiomyopathy, significant hypertensive heart disease, restrictive cardiomyopathies, and to my knowledge, I don't know that any of those effective therapies are associated with increase in the dilatation of the heart and, in general, it's not a good sign. So what is your read of this increased LV end-diastolic volume index being suggested as a potential good thing?

DR. SOSLOW: Yes, so two things. I was

suggesting that we just take echo out of the discussion. That was really why I brought it up, so apologies if people misinterpreted. The second thing is one of the diseases that I spend most of my time looking at, Duchenne muscular dystrophy, we see smaller left ventricular volumes. We still have done all the work we can to figure out what associates with morbidity and mortality. Even though they are smaller at baseline, if they dilate, they get worse.

So I'm not aware of any diseases where they start small, and if you make them bigger, that's a good thing, but I don't know if there are others out there. I mean, there certainly could be that I'm not aware of.

DR. BUTLER: Before we move on to a different topic, at what age do you not just get -- heart just normally with aging gets bigger? Is this an aging issue?

DR. SOSLOW: When you're born, you have somatic growth about 3 times the weight of where you are. Sorry, my wife's a pediatrician, and she

knows this stuff way better than I do. Your heart grows concurrently with the rest of your body, so you see growth in your heart over time. That is why we index everything with Z scores. There's no way to interpret an absolute number. When I'm reading an MRI or an echo, I have to look at what their size is so I know how that relates to them because, otherwise, it's meaningless.

DR. BUTLER: Thank you.

Dr. Gerhard?

DR. GERHARD: I think there's one other elephant in the room that we haven't discussed and honestly don't quite know what to do with it. It's this issue that there's a huge difference in the 6-minute walking distance between screening and baseline, and all that happens in the entire trial duration is really that people recover baseline in both arms. I think that's a very difficult thing to interpret. They're completely different interpretations that could all make sense, so I'd like to hear from others what their thoughts are.

Then my other question really to the group,

to the clinicians, is whether your interpretation is about the effort dependence of the outcomes because the sponsor mentioned, at some point, that in this condition, it might not be truly effort dependent because it might be somehow physiologically capped. So those two things I think should weigh in the discussion.

DR. KISHNANI: I would like, actually, an opinion also because it looks like there was at least a 2-week difference, a 1- to 2-week difference, between the screening and the baseline, so I'm not able to wrap my head around the fatigue component here. It's not like it was done on day 1 and then again on day 2, unless I've misinterpreted this.

MS. SHUMAN: I had asked that question earlier, and I think the answer is there's a 2 to 4 week delay in that they had to travel there, travel back home, and then travel back to clinic. So they're thinking the fatigue was from that second leg of a travel back to back, which is consistent with a lot of mitochondrial disease

patients with travel and conferences.

DR. BUTLER: Sorry. I realize it's repetitive, but if you can just announce your name for the recordkeeping purposes when you ask or make a comment.

DR. TUCKER: Yes. Carole Tucker. Oh, sorry. Go ahead, Caleb.

I'm a physical therapist by training in my earlier career, so I'm really familiar with some of these functional measures, as well as fatigue and patient-reported outcomes. When I really dug down into it -- I don't know what slides they are. I'm looking at the subject data listing of 6-minute walk tests for subjects. It's the trajectory across, and I'm focused on SPIBA-201, Part 2. What you do notice, and it was brought up, is that once you start the actual Part 2 trial, except for 2 subjects in 6-minute walk test, people stay relatively flat and reflecting that variability. So I think that interpretability is really hard to say about where that change is driven for all the reasons.

When I look at the very endpoints, you're down to an N of 3. So when you look at the flatness of some of these trajectories, and then at the very end of the long-term you see those changes in the positive direction, I don't know how to interpret that because the individuals having the most benefit end up staying the longest, and does that skew those longer term results?

I am impressed by the differences we see early on, so it comes back to those earlier comments that a 12 to 16 trial, and the PROs, and some of the other measures seem to be where the maximal, or at least 50 or 60 percent of the gain, is. As I look at these, I don't know how I could distinguish changes in this open-label one as to be directly drug related versus some of the study design.

DR. BUTLER: Javed Butler here. I just want to state, I sort of heard two completely opposite things during the discussions, and I just want to make sure that I got it right. On one hand, we heard that the reason why the placebo effect was

different is because the screening versus baseline, there was a big dip because of tiredness, travel, fatigue, what-have-you, and that people got back to where they were. So it wasn't like the placebo arm had a gain from a screening of 30 meters. They actually went down 30-40 meters, and then got up, and therefore, the 40-meter improvement in elamipretide during the randomize is the real improvement. That's what I heard.

I also heard that the cardiolipin ratios went down at 12 weeks and that they correlated with improvement in elamipretide related 6-minute walk test. If that is true, then there is a little bit of a discordance that 6-minute walk test improved, but none of those other fatigue measures or anything had any effect at 12 weeks. But then in the same tone, I also heard that 12 weeks is not enough and that it takes much longer time. So I don't know how people interpret that.

DR. ALEXANDER: I mean, you can explain looking back till the cows come home. I don't know that there's any way -- I mean, that's the

importance of prespecification. Caleb Alexander. Sorry. I think, Tobias Gerhard, your question was a good one, and it is plausible that this was fatigue, and travel related, and so on, and the baseline, it's really the screening value that one should look at, but you can tell another story that is just the opposite. So I think that's really why the prespecification of the protocol is so important in the first place.

I think also, just to address your other question, Tobias, which was about whether or not the 6-minute walk test is an effort-dependent outcome, I don't think anyone would suggest otherwise. I guess what I heard was that when people are really fatigued, that they hit a wall. Then I think there was some interest in looking at self-reported fatigue levels as a means to try to mitigate the validity threats that are posed by using an effort-dependent outcome.

DR. KISHNANI: Sorry. Could you repeat the last statement that you made?

DR. BUTLER: Yes. Please go ahead.

DR. KISHNANI: This is Priya. I was just asking if the last part could be clarified. I couldn't hear that very well.

DR. BUTLER: Dr. Caleb Alexander?

DR. ALEXANDER: Sure. Yes. This is Caleb Alexander again. So if you look at sponsor slide 55 -- you don't have to put it up -- essentially in trying to understand whether or not the screening or baseline measures were really the, quote/unquote, "true measures," there was a reference to the fact that at the point when they were at a nadir, the fatigue level was at a peak.

So my point was that, while I don't think one could argue that the 6-minute walk test is an effort-dependent outcome, I think there was an effort to try to better understand whether or not how much that may be at play by looking at self-reported fatigue at a contemporaneous measure.

DR. BUTLER: Dr. Shaw, you had a comment?

DR. SHAW: No. I actually think that Dr. Tucker clarified it. At one point, someone I

think was throwing down this 100-meter change, and I just wanted to make sure it was clarified, that's not what we saw, at least depending on how you looked at the data -- how I saw in that long-term Part 2 follow-up, and it was very much what Dr. Tucker mentioned. What I saw was after the first 12 weeks, things were really stable until week 168 or so, until you started having uneven measures of who was actually in the mean.

DR. TUCKER: There are 2 subjects that really still showed that remarkable increase probably from 24 to 50, but yes, that's the case looking at the slide.

DR. SHAW: Yes, I just wanted to clarify that there was a lot of stability, not necessarily this 100-meter change that was mentioned earlier. Thank you.

DR. BUTLER: Go ahead.

DR. KISHNANI: I had another quick comment. I also wonder, given the small number of patients, whether there is more of an impact in some patients versus others, and I understand that there's no

genotype/phenotype. It's a very small cohort, but still to try and see -- and I know they took out the extreme outliers, but still could it be that there are some that it responds better to than in others? I couldn't get a sense of that either.

Also, my other question was, if we want to get a better handle on the 6-minute walk distance, were any of these patients also in the natural history studies? Do we have any of that proceeding data from them to see what they looked like before they entered into the trial?

DR. BUTLER: That's a great point, but I don't think anybody in the committee can answer that question.

Any other comments related to this?

(No response.)

DR. BUTLER: I had another question for our statistical colleagues. Again, this is something that I heard two separate things. There was a large drop-off from eligible pool of 79 patients to 24 patients being considered for the extension, and the reason was that the gap was of all those

patients who would not have been eligible for the randomized trial. But then in the FDA presentation, what we saw is that, actually, there were 20 patients who were not included because there were no data available on those patients appropriate to be included at baseline or some reason.

So it wasn't that they were not all eligible, 19 included and 20 had no data, but how much is the concern about the representation of the patients that got into the long term of the entire population of Barth versus selection bias?

DR. O'CONNOR: You're jumping to question 2.

DR. BUTLER: I already have.

DR. ALEXANDER: I mean, I don't think we'd be here today if there was really profound, and compelling, and consistent evidence across all measures in the subset that were enrolled that participated. So if you're asking if there's a lot of concern about all the people that didn't, for me, that certainly isn't an overriding concern.

DR. BUTLER: Okay.

Why don't I just quickly summarize the discussion that we had on question 1. As Dr. Gerhard was mentioning, there is a little bit of an artificial distinction between 1 and 2, so we'll just continue this discussion after the break.

We started this discussion by discussing that there are some rules as to when uncontrolled studies might be reasonable to do and some of those things like rare disease and the safety concerns not being there, and the magnitude of benefit, and those things seem to be appropriate in Barth syndrome. We had a robust discussion whether the 6-minute walk test distance that was improved does meet that threshold in terms of improvement, which we consider significant enough.

We discussed that the answer was yes, that it was 3 times higher than what we would consider a clinically important difference, so the differences were large. But then there were concerns raised that there were a few patients that had significant improvement that may be dragging the mean, and that

for the overall population, maybe that was not that much.

There was a significant discussion about information bias, the propensity match analysis, and this smaller cohort with three potential variables does not really take care of confounding. Then imputation with replacing observed value with predicted value and single imputation rather than multiple imputation may have residual concerns as well.

There was significant difficulty in the interpretability of the echo data, both in terms of the echo data, but even if you take the echo data at its face value, what is the interpretation of that in terms of the clinical relevance overall?

There were then further discussions about 6-minute walk test and the placebo effect, about the placebo effect being different in the two slides and what is the impact on fatigue between a screening and downturn, and that there were really no good ways of figuring out the placebo effect, and that the randomized cohort, we have to take it

in its full face value. That did not show any benefit, and it was the extension that did show the benefit, and then there were some feasibility questions discussed.

Is there any major point that I missed that was discussed?

Dr. Gerhard, you had a comment?

DR. GERHARD: Not directly to the summary. I just wanted to make the point that there are also real selection issues in the treated group because we're following only eight of the original 12 patients. So if you have a distribution in outcomes and you take four of the worst performers potentially out, then the remaining group will look better. We haven't seen the data on the 4 patients, the two that didn't continue in the extension trial and the two that dropped out during the extension trial.

DR. BUTLER: You have a comment?

DR. PETERSON: Yes. I'll just add -- you may have summarized it -- I thought Caleb did a very nice summary of the effect is seen very early

on. The market benefit was seen early on, and then it stabilizes out, raising the potential possibility that knowing what you were on impacted the results.

DR. BUTLER: Okay. So why don't we just take a quick 12-minute break and be back in by 4, and we'll move on to question 2 at that point.

(Whereupon, at 3:49 p.m., a recess was taken, and meeting resumed at 4:00 p.m.)

DR. BUTLER: We will now move on to question 2, which is also a discussion question. This is a discussion question as well. Discuss whether SPIBA-001 demonstrates that elamipretide is effective for the treatment of Barth's syndrome. Include in your discussion the interpretability of externally-controlled study design and the findings on 6-minute walk tests, functional outcomes, and echocardiography.

So maybe I can restart. As Dr. Gerhard mentioned, there's a little bit of an artificial differentiation between question 1 and question 2, so we can have an overlapping discussion.

Dr. Alexander, can you just expand on that about your concern, or lack thereof, of selection bias of these 19 out of the all the eligible patients?

DR. ALEXANDER: This is Caleb Alexander. I understood the question would be a concern regarding whether or not these 19 are representative of how the product might work among all those that weren't selected, so I guess I'm speaking about the issue of generalizability. I was just saying that I thought that if there was very compelling evidence -- especially in a randomized and blinded setting, but even in an hypothetical scenario where there was, for example, an outcome that wasn't effort dependent, or where there was less concern about placebo effects, or any number of other features -- that I don't think it's a big deal, personally, that the product wasn't studied among all 60, or 70, or 80 individuals.

As we heard from the sponsor more than once, it wasn't like those 19 were cherry-picked or

something. There were very few -- frankly, there were only 6 or 7 more, at most -- that were potentially eligible. For inclusion, you want the natural history cohort to match the characteristics of the individuals that were in the open label, so I think the sponsor did a very nice job demonstrating the rationale and the science, frankly, behind the selection of those 19 individuals.

DR. BUTLER: Thank you.

Dr. O'Connor.

DR. O'CONNOR: Chris O'Connor. I agree with Dr. Alexander. I think the sponsors actually did a very thorough job in getting down from 79 to 19, trying to match the inclusion criteria. The other part that I think the sponsors may not have emphasized is that the natural history cohort may even be enhanced because when we do this in heart failure, there's a lot of delusional heterogeneity in those natural history cohorts.

This is a genetic homogeneous group, so many of the variables that we worry about that can

dilute and create heterogeneity are narrow because this is a very genetically homogeneous cohort. So I think that's added value to the natural history cohort, in my opinion.

DR. BUTLER: Point well taken.

Dr. Clark?

DR. CLARK: Matt Clark. I guess the thing we're all talking about over and over is the debate on what the interpretation of 6-minute walk testing is, and placebo and effort-based effects. Look, I'm a pediatric cardiac intensivist, so this is pretty far away from a ventilator, but it does have to do with physiology, which is what I spend most of my time doing. And when you look at things like respiratory exchange ratios and VCO2 or VO2, these patients are maximally exerted with very minimal effort. So I guess I still question whether that's a physiologic limitation or really an effort-based and placebo-influenced outcome when I look at these results. I guess those are my thoughts for the group.

DR. BUTLER: Dr. Kishnani?

DR. KISHNANI: Yes. I had a question about the 6-minute walk distance and how it was done in the natural history versus in the clinical trial. I know they stated it was done by the same individual, but yet there was one patient, as I could recall, who had it done 8 times, and they only came to, I think, the Barth syndrome meeting on two occasions, or three occasions. So I still question how the other five were done, or other six were done.

Again, it's more a question about how the 6-minute walk was done because if you put the two cones at 25 meters versus 30 meters in a clinical trial versus here, you get a lot of difference in your outcomes. So just, again, a question on that; and I don't know [indiscernible 8:19:54].

DR. BUTLER: Yes. I expect that in the meeting versus the clinic, there might be some mild differences, and we just have to interpret the data based on that.

Do you want to say something, Dr. Clark?

DR. CLARK: Matt Clark again. My only

experience personally as a father is when we take our kid to these places, it's the same physical therapist interacting, which I think is huge. I want to point out that the feasibility of doing this at a multisite fashion, I think the variability starts to really accumulate pretty quickly.

DR. BUTLER: Dr. Ellenberg?

DR. ELLENBERG: Yes. I've been spending a lot of time staring at slide 80 that the FDA put up, that Dr. Bai put up. On the left-hand side, it shows the observed walk values in the natural history cohort, and there's a lot of variability, and there are few of them who did have big increases. Then some of them, it may have went down. One of them only had a couple, but it stayed up.

So when I look at this, it makes me wonder about what I said before, about is there evidence that people who are untreated do uniformly poorly on the event? And from this, when I see that there's a few who actually go up, and even if they

go up and then they come down, but then maybe they go up again, the variability, it makes me wonder about that assessment; that they don't seem to be uniformly poor. That's not a direct answer to this discussion question.

DR. BUTLER: Dr. Jonsson-Funk?

DR. JONSSON-FUNK: Thank you. I had a few reflections on this specific question. I think there are a lot of strengths to this natural history study compared to many ways that these are often drawn, in that these individuals were being evaluated, essentially using the same protocol by the same people, and that it also required that patient to travel substantial distance in the same way that they would have to have done to participate in the trial visits.

I think sometimes there's sort of baked-in heterogeneity that comes from whether an interaction like this is happening at the convenience of the provider who's down the road versus involving considerable travel. So I think I appreciate that in this setting, these feel like

they're more apples to apples in a sense, that they're both after substantial travel for the patients that could have its own effects.

Then the other thing that I was using in my interpretation of this is that we have a very variable measure in the 6-minute walk test, but if we take the placebo effect that was observed in the randomized portion of this and discount the observed differences that we see in the natural history study, it still looks like there's an excess of greater than 25-30 meters gain. I know that's borrowing across these two studies but, to me, that's a useful interpretation.

That said, I agree that the concerns raised about what would the outcomes have looked like in those 4 individuals who weren't maintained and are they effectively a random sample, it would have been helpful to see their data for the period of time that they were in the population lined up and whether or not they tended to skew things up or down prior to withdrawal. Thank you.

DR. BUTLER: Great point.

Ms. Shuman?

MS. SHUMAN: Hi. This is Devin Shuman speaking. I saw a lot of the concerns others have in terms of the data and trying to use imputed data when we only have limited data points. I will say I did find the sponsor briefing materials, table 7 on page 65, helpful in comparing the different cohorts because it broke it down by many of the other secondary measures like strength and sit-to-stand.

I still am coming back to, I think, the same point of the last person that spoke about there being a significant change over a placebo that's sustained for so many years. I honestly don't have as much experience with placebo effect in clinical trials. I'm not sure if others maybe can speak to if that placebo effect is typically maintained for that long, if that is part of it.

I do think I tended to fall to the mito [ph] ex-clinicians who spoke about this being very typical for birth based on other natural history, again, limited studies of 2 dozen and 3 dozen

patients other people have published previously that didn't show changes in walk time strengths that sit-to-stand over 2-year periods, but I know you can only so much limit it and take some of that background information.

DR. BUTLER: Thank you.

Dr. Shaw?

DR. SHAW: Thank you. Pamela Shaw. I guess two comments. The first was my original comment. We talked a lot about the methods of analysis and concerns, but the thing that I did want to emphasize is when we talk about a natural history study, the ideal way we would do a natural history study is we would bring people in at regularly scheduled visits and measure them. That's a natural history study.

This one, we have data, and we're trying to maximize the data that we have on this rare condition. This was convenience data. We don't know why these points were measured, and we all think about when we go to the doctor, it's often when we're not feeling well. So that's what makes

it harder to interpret. Of course, it's different when you have a chronic condition; maybe you also have regularly scheduled visits, so maybe it's a mix. But that's what I find ultimately makes this data, that wasn't about prospectively following people but grabbing data that we had on them, much more difficult to interpret to say that it's comparable.

Then just relative to the last comment, whether you think a placebo effect can be sustained, in a clinical trial when you require people to have an impaired 6-minute walk to join, you need to not be doing so well when you join, and there tends to be a shift up immediately upon second measurement; then it doesn't retract back necessarily if it is the regression-to-mean effect. So they're on top of this in Part 2. We had a few more people who decided not to continue maybe for health reasons, then that might also shift the mean up, counterbalancing what might have been otherwise a retraction on average.

So there were multiple things going on that

I think made it challenging to interpret exactly what was a gain that could be attributable to the treatment in this uncontrolled portion. Thank you. That's it.

DR. BUTLER: Thank you.

Dr. LePichon?

DR. LePICHON: Thank you. J.B. LePichon. I'd actually like to pick up on a comment that Dr. O'Connor made just a few minutes ago.

Dr. O'Connor, you mentioned that the sponsor had done a really good job and provided genotypic homogeneity. Did I get that right?

(No audible response.)

DR. LePICHON: I'm a little confused. The reason I'm asking is because this is important to me because I think that in Part 1, part of the issues with Part 1, the longitudinal study, is that there is considerable phenotypic heterogeneity, as we know in Barth syndrome, as we have in most of our other genetic diseases, and I didn't see anywhere in the data genotypic homogeneity addressed. In other words, I didn't see any

reports of what -- all we know is that, presumably, all of the patients have pathogenic variants in the tafazzin gene, but we don't know where those variants are. So I guess I misunderstood what you meant by genetic homogeneity.

DR. O'CONNOR: Alright. That was in reference to contrasting to that if we were to study general heart failure, or HFpEF, where there would be massive heterogeneity across a natural history cohort. In a rare condition like this, my belief is that you have much more homogeneity because the characteristics of the population are much more consistent and not as heterogeneous. So you're not going to have so much delusional heterogeneity that you might have as you're studying HFpEF or HFrEF in the general population.

So it's not specific. I wasn't talking specifically that within Barth syndrome we've got a really homogeneous population -- there's heterogeneity in that -- but in contrast to other natural history populations that we studied.

DR. LePICHON: I have a question. The

biggest thing to be discussed is that the treatment arm knew definitely that they were on the treatment long term, and the natural history knew that they were not on the treatment, and how does that affect the results that we are seeing, i.e., no changes in the natural history cohort and all the changes?

One question I have for somebody that has a background in physical therapy and rehab, our sense is that there is a placebo effect on effort in 6-minute walk test; that's been discussed several times. The FDA made some comment about the hand dynamometry and how much newton power they can exert. I just want to get the committee's perspective whether the same placebo effect, the drug, can you start squeezing more strongly?

DR. TUCKER: Yes. That's a good question. This is Carole Tucker from UTMB again; two thoughts on that. It's clear that the effort, what we're hearing at least from the patient voices -- or the people with Barth syndrome I should say -- is that they really do hit a wall. That fatigue just really happens. So I expect that if there is a

placebo effect from being on the drug, it's not going to necessarily change that by 50 or 90 meters, necessarily.

For the hand-held dynamometry, one of the questions I had, which I didn't ask, is that's also dependent on the person holding it. If the person holding it is pushing a little bit -- and let's assume that they followed Primo techniques -- if it's always the same person doing that, and if they have the sense of where that person is, then there's a potential for some variability due to both sides of it, so the patient expending effort in that. And I wonder if hand-held dynamometry is better than just a manual muscle test, but there's going to be some inherent variability in that, but I'd expect to see that in both.

The one thing that I am curious about, and it just plays off on this, is that if you are in that natural history group and there were different time spans, there's going to be a portion of that natural history group that's so well connected with the Barth Foundation that they're going to be

hearing about results of the trial. So just like you have a placebo effect in the positive direction, if they're listening, and hearing, and knowing they're not on it, is there a potential for them to feel like they're not going to do as well?

Again, it may or it may not have happened, as pointed out by all of us, but we don't know that necessarily, explicitly for sure, and that makes it difficult to interpret where those things might come into effect, would be my sense.

DR. KISHNANI: I wanted to play on one fact since we have PT expertise here. Often what we have seen in clinical trials -- and here's where I think the forest plots start to help -- is everything is going in the same directionality. So hand-held, the 5 times sit-to-stand, and the SWAY application, whilst they're not the primary outcome measure, maybe there's more objectivity to those than the variability that there could be in a 6-minute walking distance. Is that a correct assumption? This is to ask the physical therapists.

DR. TUCKER: Yes. It's Carole Tucker again from UTMB. Speaking in this role, not necessarily. The fact that the primary -- and we've heard from the sponsor that that was really done at the direction or advice of the FDA, and I get that because the 6-minute walk test is considered a gold standard for functional walking. The other ones, the 5 times sit-to-stand is, I would say, a little bit newer as a gold measure, but it's pretty robust, as well as the SWAY and hand-held dynamometry.

My one concern is that this spans individuals from 12 to adulthood, so there are going to be different values for norms in kids from 12 to 18 in some of these measures. These are traditionally adult measures, and I don't know if they use the same change scores or the same values for the younger kids as the older. And the same thing with the PROMIS Fatigue, there's a pediatric version versus an adult version, so I don't know where some of the gold standardness was between the interpretation across that wider age range.

Did it include 12 to 18 or did it start at 18? Sorry. Now I'm wondering if I got myself confused. It started at 12, the mean was 19, and it went from 12 to 35. Okay. I did remember that. Sorry. So just a few things, that there's always going to be inherent noise in some of the rehab measures, but there is that trend.

DR. BUTLER: Ms. Shuman?

MS. SHUMAN: Hi. Yes. This is Devin Shuman. On this same point, what I keep coming back to in my mind is the table on page 39 of the FDA slides that showed, going back, Part 1, that actually showed no placebo change for the other findings besides the 6-minute walk, which is again something I'm thinking through, too, with this data as we talk about it. We saw such a dramatic placebo effect for 6-minute walk, but we didn't for these other measures, and these other measures sustained the change as well in the natural history comparison we have.

Also anecdotally, I found it interesting you're talking about could people who are in the

natural history know that this is going on and affect them? I have anecdotally seen in other conditions where it has -- and again, we can't guess -- the opposite effect, where they see their friends doing more, so then they try to do more themselves and push past the limits they maybe had set for themselves, as people talked a lot about the depression of having a condition and not trying; not to say that I think that's what happened, but just to throw out another. It's really hard to predict when there are these kinds of factors in such a small community where they are all probably friends with each other. It also makes it hard to blind anyone because people are comparing side effects, so it often is figured out pretty quickly, even if we try our best.

DR. TUCKER: Carole Tucker from UTMB. I just want to ask one quick question of our statisticians and other clinicians. As I was reading through the briefing materials, there was discussion about why not do a withdrawal trial, and hearing some of the compelling changes and also

what I would consider almost reversibility maybe in some of the individuals that had restarted, is there a reason why? Because I could see an RCT could be hard perhaps in this group for the reasons we've all discussed. What about that concept of the withdrawal trial? Is there a logic behind why that wouldn't be perceived as a value?

DR. BUTLER: And if I can ask an extension to that question, I think the answer we heard was that there were 8 individuals in the extension, so withdrawal would be like four in each arm or something like that. So could we really get some reliable answers?

DR. ALEXANDER: I had asked it earlier. I guess my understanding was that this was a comment not with respect to those eight but regarding a new randomized withdrawal trial. And what I heard from the sponsor was that they were concerned that there was not sufficient statistical power. We didn't hear, and I would have liked to know from the sponsor, their beliefs about how quickly the effects dissipate.

We've talked about how quickly they seem to appear, at least in the open label. After blinding has been lifted, there was this very pretty pronounced effect within 12 weeks of the open label, but in the open public hearing, we heard from several participants that said that they were aware of and felt a profound change quickly once the medicine was discontinued, and time permitting, I would have been interested to hear more from the sponsor regarding their beliefs, not regarding how quickly they think it takes for the product to work, which they said 6 to 9 months -- which we've just discussed, and I think the FDA has analyses that suggest that if it works, that it might work much sooner -- but how quickly they believe that it takes for the effects to dissipate.

MS SHUMAN: Yes. This is Devin Shuman speaking. I would echo those same questions. I wish we'd heard a little bit more about some of even the cellular and animal models about the washout period there because I know they talked about there being a delay in effect and how they

were taking that as confirmation of why the shorter trial didn't work. But how much have we tried that to see how long it would really take to unmodel possibly the repair being done to the heart that was at least hypothesized as part of the ongoing benefit?

DR. BUTLER: Dr. Peterson?

DR. PETERSON: Yes. Just briefly, the only other challenge I see with the withdrawal trial is if patients know pretty quickly which drug they're on because of the the skin response, you've got a problem. So unless you have a better blind for the alternative arm, it would be tough to do this without getting around that.

DR. TUCKER: But you could do that.

DR. JOHNSON: I was just going to add, I think you're going to have similar issues because of that, both because of folks talking to each other and knowing the effect that they had from before; but also hearing the public comments earlier, it's hard for me to imagine you're going to have a lot of people volunteering to be ones

that might come off of it. I don't know if that's true or not, but that would be my worry.

DR. KISHNANI: This is Priya. I have a question, really, for the FDA. This natural history, does it even meet the definition of the criteria for a natural history study? It's like a convenient sample rather than what we would call a natural history study, or am I off base here?

DR. BUTLER: Dr. Gandotra, do you have an answer?

DR. GANDOTRA: Thank you for the question.

Dr. Jae Joon, would you like to take that question?

(No audible response.)

DR. GANDOTRA: If not, I have Dr. John Concato taking the question. Thanks.

DR. CONCATO: Thank you. John Concato, Office of Medical Policy, CDER, FDA. I would say it's more important to look at the data and the design, and whether or not we've met the bar for substantial evidence of effectiveness. Whether we call this a natural history study or not, or

something else, it is of interest but not fundamental to the question at hand for the committee. Thank you.

DR. HONARPOUR: This is Narimon -- if I can make one comment -- with Amgen. In listening and reflecting on all these comments on the vulnerability of any one dimension of the data that has been seen in this study, and in some cases the vulnerability of any single study, it really does merit reflection that this population is incredibly small. I think we would all agree on that. I think we would all agree that the data in such cases is always going to be variable. It's going to be very difficult to get around that. We have the additional compounding complication that you expect there to be changes as people age on the study itself.

So in trying to come up with how one could feel assured that you developed very compelling and convincing evidence in this population from a sponsor's perspective, I just wanted to share it. That's an incredibly high bar to set for this

population, and it brings me to wonder what is sufficient information of effectiveness in this population rather than what is the most conclusive data for this population. Thank you.

DR. BUTLER: Thank you.

DR. JONSSON-FUNK: If I could just add to that -- Michelle Jonsson-Funk here -- I think one thing that is worth noting is that randomization is effective at balancing measured and unmeasured covariates only on average and with large samples. We saw it in the randomized component of this, that randomizing 12 people created fairly large differences between the two groups at what their baseline walk scores were, and there's no reason to expect that we would magically balance all of these covariates by randomizing a small number of individuals, and given the nature of this disease, there will never be a large number of individuals who can be randomized.

So between that and the unblinding issues, I guess I'm acutely aware that some of the benefits of randomization that we really lean on for those

kinds of clinical studies may not be achievable here.

DR. BUTLER: Thank you.

Any other comments on question 2, discussion question 2?

(No response.)

DR. BUTLER: Okay. Since we've heard all the comments, let me see if I can summarize this discussion. We started the discussion with, first, some comments related to the eligibility criteria and whether there are any concerns about representativeness of the population; and the general feeling was that there were no particular concerns about the population being representative from the larger cohort that was taken. There was a comment made that as opposed to other chronic diseases, if anything, the variability in the disease is less, and the sponsor has done a pretty good effort in creating this cohort that was followed.

There were also some comments made about sponsor's effort in actually getting the data and

whether the data are gotten at clinical interface or whether it is at some other venue that was a very good effort. In terms of the variability, nevertheless, there were some comments made that we're not particularly sure whether there is, nevertheless, residual phenotypic and genotypic variability in these patients.

There was continuing discussion about how much of the changes that we are seeing is related to physiologic peak and nothing can be done versus the lack of effort, and that is something that we just cannot definitively answer in this particular meeting. There was variability seen in both arms, so there was no, really, [indiscernible - 8:46:05] concession. There were a smaller number of patients in each arm, but within the smaller number of patients, there was no consistent effect either in the placebo or the treatment arm, and there was significant variability inter-individual overall, which raises some concern about noise as well.

There was a comment made about the 6-minute walk test and whether all the other tests were done

exactly the same way, if something was done in the clinical setting versus the nonclinical setting, and whether or not there could be some noise related to that as well.

There was actually a pretty good discussion about the placebo effect, and there was some comments made that the placebo effect is unlikely to last for such a long time; that even if there was an earlier placebo effect seen, that maybe it will wane over time. But then there were other comments made that usually people are included in this study who are not normal to begin with, there is some regression to the mean, and actually, in other disease states and clinical trials, the placebo effect seems to be maintained in the long run.

There was also a comment made that if you were to borrow the placebo effect from the randomized trial and subtract that from the long-term cohort, the residual benefit that was seen is still substantially higher than what we would qualify clinically as a minimally clinically

important difference. Even if out of the 90-100 meters, if one were to take out 30-40 meters, you'd still have a residual 60-70 or 50-60 meter benefit that is pretty significant.

The placebo effect that was seen with 6-minute walk test may or may not be applicable to some other measures like hand dynamometry. Having said that, the fact that there were multiple other tests all going in the same direction and, on one hand, are co-linear, if one thing is getting better, then maybe the other things have overlapping physiology and not necessarily distinct domains; but on the other hand does give some certainty that it is not just one of results and that multiple things are getting better.

There were concerns about the natural history cohort being a convenience cohort and doesn't really meet standards for what a good natural history cohort would be, which will be much more according to a prespecified plan overall. There were significant discussions related to what is sufficient evidence in this disease state; that

even if you were to do an RCT between the unblinding and small numbers -- and even randomization does not really guarantee with the small numbers -- that all known and unknown confounders matched. We should look at this issue with a view of sufficient evidence because definitive evidence will be very difficult.

Whether a withdrawal study is feasible and whether a withdrawal study will give us the answer or not, there was some variability in comments between the smaller numbers; otherwise, as well, the logistics of the withdrawal study, people volunteering for the withdrawal study, and the cutaneous reaction, all of those things will perhaps make the withdrawal study a little bit more difficult as well.

Any other comments in the summary that I missed? Yes, Dr. LePichon?

DR. LePICHON: J.B. LePichon. There was a substantial discussion also that applies to this part, although we talked about it quite a bit in the first part, which is the issue as it relates to

the propensity scores and the imputed values.

DR. BUTLER: Yes. In the previous discussion, we discussed single imputation, not multiple imputation, taking a predicted value rather than an observed value, and that propensity matching in the small numbers with three variables does not really take care of the concern for confounding and bias. Absolutely.

Any other comment before we move on to question number 3?

(No response.)

DR. BUTLER: Okay. So we'll now proceed to question 3. Discuss the extent to which other data, nonclinical data or other clinical study results, support the effectiveness of elamipretide.

Is there any comment or question regarding the wording of the statement?

DR. TUCKER: Does this include any of the anecdotal information we heard?

DR. BUTLER: Yes.

Hearing none, maybe we can proceed with the discussion.

Dr. Peterson?

DR. PETERSON: I'll take the liberty of doing the summary quickly, in my mind at least. This is where there's the greatest discordance, at least in my mind. On the one hand, we have somewhat disappointing results from animal models, which would be an objective way to show the effectiveness. The mechanistics work didn't do a whole lot to support it, at least in my mind, and we have issues with regards to we haven't yet heard it from use of this drug in other settings. All three of those could have provided strong empiric evidence to support it.

Against that, we have incredibly compelling anecdotal information that's coming from actual patients who are taking it, and it's seemingly uniform, and compelling data from the doctors who are using this drug in their practices, and that's seemingly uniform, and it's troubling that you could get this much discord, but it is what we have.

DR. BUTLER: One fundamental issue is that

although in the introductory comments by the FDA, Dr. Joffe mentioned that there is flexibility within this framework, technically speaking, these other data are supportive if there is one adequately well-controlled study. And in this particular case, we actually don't have one adequately well-controlled study because the randomized-controlled trial did not really meet the bar for efficacy. On the other hand, it is really difficult to ignore all the individual cases and the expanded program data that we are getting.

Dr. Alexander?

DR. ALEXANDER: Yes. I don't think I disagree with what you said -- Caleb Alexander -- but it is the case that there is historical precedent for a historical control serving as a single adequate and well-controlled study. I just want to put that out there that it's not as if one has to have -- because the randomized blinded trial did not succeed, that necessarily there's not precedent for approving a product based on -- a product that's been studied with a

single-arm study with a historical control providing adequate, well-controlled evidence.

DR. PETERSON: Caleb, correct me. I don't know this case as well as you would. Has it ever been that an historic control has trumped the randomized trial, meaning that you have a randomized trial, it failed. You have an historic-controlled study that was done, and now we take the historic-controlled study because of characteristics of the study and have that overrule what we saw in the randomized study.

DR. ALEXANDER: I'm going to defer to an FDA historian on that one.

DR. STEIN: I'm not sure we have an FDA historian in the audience here, but let me just make a couple of comments. I do want to just point out that in the regulations, there are a number of different designs that are considered potentially adequate and well-controlled trials. Now, Dr. Joffe at the beginning of the meeting presented some of the characteristics that need to be met for a trial to be adequate and well controlled, but to

remind you that a placebo-controlled trial, an active-controlled trial, an externally-controlled trial can all be formats that are potentially adequate and well-controlled trials.

With regard to weighing the randomized, blinded, placebo-controlled trial relative to the potentially externally-controlled trial or baseline-controlled trial, that was the 201, Part 2 or the 001 trial, respectively. What I would say is you need to look at the design and nature of each of those trials. Certainly, we've seen trials that have very good explanations for why the trial was not designed properly to be positive, and then a subsequent trial designed more properly could be positive.

So we really want to hear from you how you weigh those two components and consider each of them in your assessment of effectiveness. But I just wanted to emphasize that the designs that can be considered adequate and controlled include external controlled, as well as baseline- or historical-controlled trials. Those are

potentially adequate and well-controlled trials, and I would just refer you again to the criteria that Dr. Joffe presented in one of the early slides.

DR. BUTLER: O'Connor?

DR. O'CONNOR: Chris O'Connor. I'd like to complement those comments, and that is if your randomized-controlled trial has deficiencies, then the non-randomized-controlled study I think could trump a deficient randomized-controlled trial. That's where I potentially am here, is thinking normally we'd put the randomized-controlled trial way at the top, but can we with this trial, which is trying to do something that's really hard to do, a randomized-controlled trial with small numbers; high degree of variability; and if you look at their statistical assumptions, they were pretty broad, 80 percent power, 50-meter walk; so I agree with the comments you made.

DR. BUTLER: Dr. Ellenberg?

DR. ELLENBERG: Well, I'd like like to just repeat a discussion I had at one time with

Dr. Robert Temple, who was, for many, many years, the great guru of clinical trials at the FDA. I was recounting to him my argument with a colleague about how flexible the FDA can be, and I said, "I told them that if we had a first-in-human study in advanced cancer of the pancreas, and of the first five in that phase 1 study, four of them had a complete response that seemed to last a little bit, the FDA wouldn't say you have to go do a now comparative trial with another drug; you'd say do another 5 patients, and we'll approve it." And Bob said to me, "We wouldn't even tell them to do another 5 patients."

So what's the control in that? It's the literature. It gets back to the example that I gave before about you know the natural history, you know that these people are not going to have spontaneous complete responses. So that's what has been the issue for me, is how confident are we that the uncontrolled experience, the experience of untreated patients, is so uniformly poor.

DR. BUTLER: One thing that I am also

struggling with is how variable is the natural history of this disease. What we heard today is that there are dramatic life-saving benefit in really young kids, and infants, and at birth, and early diagnosis, whereas in the older population, if I heard it correctly, there are not a whole lot of hospitalizations or clinical events, but it's mostly symptoms, and fatigue, and those kind of things, and that variability is a little bit striking to me. In other words, if there is a drastic clinical course in a young kid, should we take that data and equate it to an adult, where the primary issues are symptoms and physical limitation for which we have all these concerns about the study design?

Dr. Johnson?

DR. JOHNSON: Jon Johnson, Mayo Clinic. I think that gets at the exact issue of Barth, where you have this cohort that gets really super sick as neonates or young kids, and then whether or not there's a treatment mechanism, which is not necessarily what the data were being presented is

about but also comes up when you're trying to think how you would best move forward with it.

I don't know. A summary of the people who've been able to get the drug open access would be helpful, and then giving us more data to work and pushing us towards something here. But it sure seems like we're getting a lot more data from the public comments and from these anecdotal studies that is really, really hard to ignore, even though I don't have the data in front of me on a slide that shows in any of these studies that it would be a slam-dunk.

DR. ALEXANDER: There's enormous variability. Think about the example that we heard of a child that went from ECMO to discharge in 9 weeks. Perhaps that's the effect of the drug, but then that's hard to square with the results of a trial that didn't show any separation of groups over a longer amount of time. So I think that the natural history -- frankly, the previous data that we've seen that's been published thanks to the hard work of clinicians caring for these

individuals -- demonstrate that there's enormous variability, both across and within individual patients.

DR. BUTLER: Ms. Shuman?

MS. SHUMAN: I think Tobias actually had his hand up first, but I can go. Yes, I think what we're talking about here is really what it keeps coming back to for me, in that it is just a rock in a hard place for ultra-rare conditions, where we only have so much information. Sadly and just in the way of the world, the first study done was the study that was trying to establish how do we even look into this condition, what base marks do we have, and a lot of these details. I think that's a really hard place for any group to be, and for the patients to be as well.

To me, I do keep coming back to the regulatory flexibility of what can we do from here and kind of ignoring the patient voice to some extent because there isn't that hard data for it, but also not wanting to ignore it because they're telling us the reality from a much broader

standpoint if it has been a couple dozen people put on this.

I think I would maybe disagree a little bit with some of the comments about this condition not being well understood, though. It does seem to be a very consistent message in the literature and from every clinician who's worked intimately with this condition, including the only center of excellence for this condition in the United States, to see the vast majority of the patients; that what they are seeing is unprecedented, and it's not following the natural history they've ever seen in the last decade of their careers.

I think that that evidence does need to be taken with some weight, even if it is hard to nail down any evidence when it comes to symptoms that are in a honeymoon period, where the heart isn't changing too much and the main symptoms are subjective ones that arguably will never not be subjective in terms of things like fatigue measures. We've yet to find a biochemical way to trace that in any helpful manner, and may or may

not be able to find that in the next 5 or 10 years, even if we try our hardest to; and so, where does that leave us? Thanks.

DR. BUTLER: Thank you.

Dr. Gerhard?

DR. GERHARD: Yes. I'm picking up where the last speaker left off. From my perspective, looking at the data, it's just a true uncertain situation. We don't have the data we need to make a clear decision. There are points, data points, pointing in one direction and in the other direction. So what does one do in the context of uncertainty in such a rare disease?

There are really two questions. One is, are we likely to get better data in a reasonable time frame? And I have some concerns about that. Then the other is, what do we do in terms of the action in a situation with such uncertainty? Which I've never seen in a context like this. This results in a question for FDA. What do you want us to vote on, whether the evidence is conclusive or whether we want the drug to be approved?

(Laughter.)

DR. STEIN: Peter Stein, FDA. Let me step back because I do think it's really a critical question, and I'm not sure I can give you the perfect answer, but I can tell you how we will also, of course, struggle, and have struggled with data of this sort.

When we say regulatory flexibility, what we mean is we recognize the fact that you can have the same level of certainty in a disease, like a drug for type 2 diabetes or asthma, that you would have for a disease that has 100 or 150 patients in the United States. That would clearly be inappropriate, and we don't expect that level of certainty. On the other hand, I think we all want to be in a position to approve a drug that we conclude and can have some confidence that the drug is effective.

So what we're asking you is to recognize the context, certainly not look at this with the same lens that you would look at a drug for a very common cardiac condition, to prevent myocardial

infarction, for example, but to consider that this is in the context of a rare disease, but also to recognize that I think all we want is to make sure that when we're treating a patient with a drug, that we have some belief and some confidence that that drug provides the benefit that it purports to have. So yes, we certainly will accept some uncertainty that we would not perhaps accept in a different setting, but we also want to be able to conclude that the drug is effective.

DR. TUCKER: Just a quick question while we have the FDA answering. I have two questions, and it's, again, kind of related to process. One of the things we've been hearing is about the time to data collection and the urgent need. We've also heard from the sponsor that they are willing to do a postmarket, maybe -- or post-approval, whatever the logic is -- study. So I'm curious as to what is their obligation to carry that out, and if that study does or doesn't provide compelling evidence, is there a back track?

One; and then secondly, we've heard a lot of

anecdotal stories about the effect in infants, but none of the data we've been presented so far in either of these studies include infants or children left [indiscernible - 9:07:00]. So for that, I'm looking at this like, well, there are no studies, but there's a ton of compelling evidence. And again, within that breadth of it, if we say yes today, does that include all ages, or is there a hedge there?

Do you see what I mean? I worry about the lack of data in infants, even though it seems most effective there maybe.

DR. STEIN: I think you've asked several questions --

DR. TUCKER: Alright. Carole Tucker from UTMB. Post-whatever decision --

DR. STEIN: Peter Stein, FDA. I'll try to answer I think several questions in there, but I want to focus on the first question about postmarket. Under the pathways of approval, we talked about accelerated approval and we've talked about what we call traditional approval. Some

people say full approval, but traditional approval. In that context, we expect that the evidence will show that on a clinically relevant endpoint -- we talk about endpoints that improve how patients feel, or function, or survive -- that in that sort of approval, the evidence needs to be available at the time we approve the drug that shows the drug has that effect, so that can't be parsed and part of that coming after the approval.

In the accelerated approval pathway, where we use a reasonably likely surrogate or an intermediate clinical endpoint, that is a setting where we haven't confirmed that that surrogate absolutely demonstrates clinical benefit. We have surrogates that do that like LDL cholesterol, but in the setting of accelerated approval, there is a commitment, there's a requirement, that there be a study afterwards. It's a postmarketing requirement that there be a study that confirms it verifies the clinical benefit even though there has to be substantial evidence that the drug affects the surrogate. So back to your question with regard to

traditional approval, at that point, we need to approve the drug, and we need all the evidence in front of us that demonstrates the effect on that relevant endpoint.

Now, in terms of labeling, I'm going to be very vague here because, of course, this is downstream, but what I would say is that we don't necessarily label drugs in exactly the population that it was studied in. We can go beyond that, but we have to be able to generalize to the broader labeled population with the evidence we have in front of us. And if there's not evidence, for example, in a different form of the disease, or an age where there could be a different outcome of the treatment, the label would typically be narrowed to that population where we have sufficient evidence to be able to broaden and generalize to that.

I hope that answers your question. I'm happy to clarify if I didn't.

DR. TUCKER: I think it does, but just on that last point, I get the generalization. And again, can anecdotal evidence that this has a

remarkable effect in infants, in a positive direction, be considered part of the data in terms of it extending down there? For instance, if I don't see study data that says that it works in infants, that would influence my decision if you're going to tell me that it could.

DR. STEIN: Peter Stein, FDA. What I could say in general terms is that where the diseases are highly similar, we certainly can try to expand the labeling. Obviously, there's other information that will be required in pediatric patients to extend into that population. But particularly where the disease isn't the same, it presents very differently, we would very likely in that kind of setting expect data that shows that it benefits that different population when the disease isn't presenting in a similar way.

So if the population presents very similarly, we might conclude that that gives us enough confidence that the drug would have a similar benefit. If it presents very distinctly in a different format, different organs involved, we

would expect to see data that shows that, indeed, in that separate population, the treatment would have a similarly beneficial effect.

DR. TUCKER: Super. Thank you.

DR. SOSLOW: I just want to point out that as a pediatrician, when I look at it, there's labeling and there's prescribing, and most of what I prescribe is off label. So if it is approved, even for just adults, and we think it will help a neonate who's in distress, we will get that neonate the drug. So from some standpoints, the labeling is a little less important here once it's approved. I'm probably oversimplifying things from your standpoint, but that's the way I kind of look at it.

DR. KISHNANI: Yes. This is Priya. I would tend to agree with that statement. There will be a lot of off-label use. And the point is, how do we collect those data in a systematic way for safety, or for efficacy, or looking at it more from a cardiac standpoint or other endpoints? I know there are postmarketing commitments or

postmarketing requirements. How does one ensure? Because for the better good, it is important to get these data.

MS. SHUMAN: This is Devin Shuman speaking. I'm going to talk on something that overlapped with that as well. For me, a question that I think some of us are dancing around, but is inside the FDA definitions for what should be considered for substantial evidence and the different options, is ethics. And maybe this is the genetic counselor hat that I wear, but I think it's important to balance out or ask ourselves both the ethical question of, if we're approving something based on data that we're not sure of, what is that doing to an ultra-rare community and population of people that are maybe spending lots of money jumping through hoops, putting hope into something that may not be what we think it is or we're assuming it is?

Also, on the flip side, I think a lot of these discussions with the withdrawal studies do come down to the equivalence series of, is withdrawing care the same as not providing it to

begin with? And while there are, obviously, entire ethical debates on that topic, I think as a rare disease provider, to me, it does feel very different to take away an only treatment for a group because their condition is not as well understood compared to not providing it to begin with. And at this point, they've said that at least a fourth or more of the community in America, maybe up to a third or or half, are potentially on this drug already or heading that direction through EAP approvals.

So what does that mean for our considerations? I'm not trying to imply that we should lower the bar because I think that's the other side of that. We have to make sure we're not lowering the bar out of emotions and creating an ethical dilemma there as well.

DR. KISHNANI: To that point, Devin, I have another point also. Does that also limit the ability if there's another drug in development? Now you've got to compare to what is approved. So establishing some information, even if it's in a

postmarketing setting, really needs to be done so that it allows the field to grow and that we don't stagnate because now we've got an approved treatment.

DR. BUTLER: Dr. Jonsson-Funk?

DR. JONSSON-FUNK: I wanted to share a concern when we're talking about off-label use in pediatric populations about insurance coverage for this. I know that's not under FDA's purview directly, but if we believe that this drug being approved by the FDA would then lead to its access for the infants, who we have heard have benefited remarkably from it, I'm concerned that that might not translate to the extent that insurance doesn't agree to cover that. I just wanted that awareness of the cost impact of this to be out there.

DR. BUTLER: Thank you.

Any other comments related to -- Dr. LePichon?

DR. LePICHON: J.B. LePichon. It seems like we've gotten pretty far off topic, which is I guess ok because it's been a rich discussion. Following

in the line of that discussion, since apparently we're looking at considering whether to move forward with approval or not and what it would take, a couple of thoughts.

The first one is, we know something about the natural history of this disease from the work that has been done. We know that in infancy is when the most dramatic clinical progression is going to happen. We know that then they tend to somewhat stabilize or plateau until teenage years, and we also know that there is considerable phenotypic variability, with some patients living into their 50s and 60s and 70s, and others not.

So it makes me wonder, are we looking at the wrong patient group in this case? We've seen this happen. We've seen this with SMA, we've seen this, I would argue, with omaveloxolone in Friedreich's ataxia. We've seen this in Rett syndrome with trofinetide. We've seen it with MPC. If you catch the kiddos past that peak worsening clinical period, you miss that opportunity, and then you end up in that plateau where you have to follow them

for years to see an effect, and it becomes incredibly difficult.

The other thing I've heard is, well, it's impossible to capture these infants in order to do this study that you're proposing, and I would argue that I don't think that's true. For example, there's been some work done with -- granted, it's gene therapy -- AADC deficiency, and they put in place a huge program to try and capture those kiddos in infancy, in the NICU, so that they could start the treatments, and AADC deficiency has an incidence and a prevalence very similar to Barth syndrome; so just putting that as a thought out there since we've been discussing this.

DR. BUTLER: Thank you.

Dr. Honarpour?

DR. HONARPOUR: If I can just make one comment to that point, it's a true point, but the issue of the practicalities of executing on that come into play here in a way that directly affects the patient. So it strikes me that the anecdotes that we've heard today, for example, represent a

sizable proportion of all patients with this condition, at least in the United States, that bears some weight. Many of them want to continue the therapy and if the sponsor is going to pursue an aggressive, large program as you suggest to try to capture the patients at the right place at the right time, you have to wonder if it's practically possible for the sponsor to do it because it's a private enterprise. That may not be favorable for the patients that are already on the medicine.

DR. BUTLER: Okay. I think we can wrap up question 3. So what I heard was that at many different levels, we have these competing thoughts that make the decision making a little bit difficult. We have some basic science data, some RCT data, some other disease state data that are not as attractive, but then we have the natural history data with long-term follow-up data that is very attractive. The clinical benefit, and the Expanded Access Program, and the data that we see in young kids are very much in favor of potential benefit.

We had a little bit of a discussion about the natural history variability that led to this discussion about what are we looking for. Are we looking for definitive proof? And again, there was a robust discussion. The FDA gave their perspective as to what they're looking for. I don't think that anybody is looking for most definitive evidence, but within the data that we have, whether the drug should be approved.

There was a discussion of ethics going both ways. There are significant logistic concerns about being able to do a second study, the ethics of doing the second study, the ethics of taking the patients off the drug, and all those kind of concerns. Then on the other hand, there are also ethics of off-label use. Even in adult use, you're talking about lifelong therapy with data that if you're not certain, then based on emotionality or case reports, whether that's the right direction to go into. So all of those, we had significant discussions.

There was also a discussion that the most

compelling data comes from young infants and kids, but that was not studied, and it may be natural history variability, not stable but relative stability at later stages where the patients were studied. There were other concerns about coverage that were raised as well. The logistics of doing the study in newborns or infants, there may be some precedents in other disease states as well, but also the point was made that, nevertheless, it's very, very difficult to do.

There was also a comment made that there is precedence that historical control does amount for an adequate, well-controlled study, but then there was also a discussion, not in the presence of a randomized-controlled trial, trumping the randomized-controlled trial; then a further digging down that direction of what if you believe that the randomized-controlled trial evidence was not of the highest caliber for some reason or another, then do we learn more on historical control?

Anything I missed in the discussion for question 3?

(No response.)

DR. BUTLER: Okay. With that said, we will now proceed to our last question, question 4, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who has voted will state their name and their vote in the record. Please give the reason if you have voted for approval what was convincing to you, and if you have voted no, then what further steps should be taken.

This is the question 4. Based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome? Please provide the rationale for your vote.

DR. ALEXANDER: I have a question --

DR. BUTLER: Yes?

DR. ALEXANDER: -- for the FDA. So this comes up all the time, and it would be helpful if you could clarify -- this is Caleb Alexander. Tobias Gerhard already asked one distinction, but I'm going to give a third.

Effective, do you mean effective based on the regulatory threshold of substantial evidence, or do you mean do we want the drug to be approved?

DR. STEIN: So what we're really asking is -- we've had a lot of data presented here, and we're asking for you to put that together and determine in your mind whether the drug is effective within the context of the discussion we had about regulatory flexibility, in accepting some uncertainty. But the question is, does the evidence, as you put it together, support a

conclusion that the drug is effective? We're not asking this as the regulatory framing. We will put it into the regulatory frame as we hear your comments and read your comments. The minutes are available as well, which we do, because we really want to understand how you're thinking about this.

So what we're really asking is looking at the evidence that you've seen today from the various trials, the nonclinical data, the clinical data, the extension data, the randomized trial, how do you integrate that together in terms of a conclusion of whether the drug is effective or not.

Does that answer your question?

DR. ALEXANDER: It sounds like 1.5 kind of, but, yes, that's fine. Thank you.

DR. STEIN: And not the third option. That's a different question. What we're really asking here is do you conclude this drug is effective?

DR. KISHNANI: This is Priya. I also have a question. When we talk about approval, could it also mean conditional approval or is this a full

approval kind of thing?

DR. STEIN: Just to be clear, the approval on the table is a traditional approval. The endpoint is a clinical endpoint, so we're looking at a traditional approval. We don't have a conditional approval; we have what's called accelerated approval. But the data that you've been presented is looking at clinical endpoints that have been evaluated in these studies, and whether that supports traditional approval is really the question that we'll face. And what we're asking you is, on those endpoints, do you conclude that the drug is effective?

DR. BUTLER: Dr. Cavazzoni?

DR. CAVAZZONI: Patrizia Cavazzoni. Adding to what Dr. Stein just replied about what we would like you to vote on, when you think about effectiveness, I would also like to bring you back to the earlier comment about regulatory flexibility, and the fact that in a disease such as this one, in a ultra-rare disease, we accept a greater degree of residual uncertainty compared to

a high prevalence disorder.

DR. BUTLER: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, a light may continue to flash. If you're unsure of your vote, you may change your vote. Please press the corresponding button before the vote is closed.

(Voting.)

CDR BONNER: We're currently waiting for the temporary voting members who are participating virtually to submit their vote.

(Pause.)

CDR BONNER: LaToya Bonner. I will now read the vote into the record, 10 yeses, 6 noes.

I will now turn the floor back over to our chair.

DR. BUTLER: Now that the vote is complete, we will go around the table and have everyone who

voted state their name, vote, and we would really appreciate that you give the reason why you voted the way you did.

Carole Tucker?

DR. TUCKER: Note, the bad thing about having a first name that begins with a C. This was a really difficult decision. When I looked at the criteria for regulatory approval of a well-controlled, an AWC, and compelling evidence, I don't know if the case was made for me that there was an AWC based on that strict-sense definition. I don't think the sponsor necessarily provided that level of evidence without that consistency.

However, given the fact that we have regulatory flexibility, given the ultra-rare nature of this population, that variability we saw in the measures really could have gone either way. We did see a trend towards the positive and very clearly heard that there are dismal outcomes without -- I can't say this -- the drug, and just the hope of being given that drug may have been a reason for some of these individuals to be here.

I did have concerns about not having any experience or data in infants, as I had mentioned during the discussion, but I did overall feel that the anecdotal evidence and the trends seen just snuck it over the line to a yes for me. I'm looking forward to their promise of post whatever process data to come out.

DR. BUTLER: Thank you.

Let me jump to Dr. Peterson, who has a flight to catch.

DR. PETERSON: Yes. This was worse than our national election.

(Laughter.)

DR. PETERSON: My name is Eric Peterson. Sorry. I think the last statements were pretty spot-on for me as well. Obviously, their randomized trial was negative, and as my comment said earlier, other empiric evidence that you would want are lacking. That said, I was swayed by the preponderance of the evidence, albeit all imperfect, that fell on the side of supporting the drug, the evidence from the extension trial, from

the historic controls, each having individual flaws, but a pretty big effect, and then the predominance of responses from the community and from the physicians who are treating these patients. Given all that, better to be wrong than right here.

DR. BUTLER: We might as well then actually go down on that side.

Dr. Soslow, if you can state what did you vote, and then your reason.

DR. SOSLOW: Yes. Sure. Jon Soslow. I voted yes. My reason is complicated, but I definitely agree a lot with what Carole said. I was disappointed that some of these patients were on this drug for 7 years and not more was done, and I felt like some of that disappointment falls on the sponsor. Some of that probably falls on the FDA, too.

I think that there's been a lot of difficulty in how to deal with rare diseases. I'm not sure that this met the bar that I would have wanted -- or, sorry. I'm not sure I met the bar

that you guys usually ask for, is really what I should say, but I think there needs to be a different structure for rare diseases. When there's 150 patients with it and such a preponderance of subjective evidence saying that they're doing better, I think in that situation, as I said, we need to use the flexibility here, and they should get the opportunity to take this drug.

DR. BUTLER: Thank you.

Dr. Berry?

DR. BERRY: Yes. Gerard Berry, Boston Children's Hospital. Well, this was just impossible. I mean, it's an incredibly rare disease, and it's so difficult to get patients involved with the studies in the United States. It just seems, to me, that this is an instance where you had to look at these other factors, and for me as a pediatrician and metabolic specialist who's cared for these patients, to deprive somebody of being able to get the medicine that might help, it's just untenable for me. And my name's spelled wrong, too. I somehow became a Gerhard.

(Laughter.)

DR. BUTLER: For the record, Dr. Berry voted yes.

Dr. Johnson?

DR. JOHNSON: Jon Johnson, Mayo Clinic. I voted yes as well, primarily based on the preponderance of the nonclinical evidence. It does seem from the data that we're going to see effectiveness. If there was a "yes but" option, I would have voted that; it's yes, but I really want more data, and I want more to learn.

DR. BUTLER: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: This was very, very difficult, and I was really torn here. But I voted no because I felt like the most compelling thing that we heard was from the people who spoke in the open public hearing, and it's hard to know what to do with that. I've been involved with clinical research for a very long time, and I've seen many examples where people were given a treatment, mostly in surgical kinds of things, where they felt

enormously better and swore up and down that their life was changed, and when a randomized trial was done, there was no effect.

So I don't know how much regulatory flexibility the FDA is prepared to implement here, and whatever decision they make, I'm not going to be unhappy about it because I'm really in the middle. I do think that there is more that can be done. I don't know how many of the people who didn't participate, who were in that natural history study and who didn't participate in the trial, I don't know how many of them are taking the drug now. If enough of them are not, I think some kind of study could be done.

I think a randomized withdrawal study could be done. I'm not too worried about the amount. Yes, it will be low power, but if there's a big effect -- there's always good power for some effect, and I think that's worth trying.

DR. BUTLER: Thank you.

Dr. Clark?

DR. CLARK: Matt Clark, Children's of

Alabama. I voted yes. I'm voting as a cautious and optimistic father. At some point, forest plots and a lot of trends turn into what they may represent here, which is possible evidence. As a cardiac incentivist, the next kid that comes in at 2 a.m. crashing on the ECMO, you're probably going to get an emergency IND for this drug and that situation, and question 3 was where I landed on this, is favoring approval.

DR. BUTLER: Thank you.

Javed Butler. I voted no. This obviously was a very difficult decision, as everybody has said. Before I give my rationale, I just really want to thank the sponsor for taking on this rare disease, not an easy thing to do, and the journey that they have gone through over the last decade, and also the Barth Foundation that they have tracked and are following more than 90 percent of the patients. This is absolutely remarkable. I also want to thank the FDA for giving their very nuanced interpretation and opinion of the data.

Finally, what made me make my decision for

no is the fact that it looks like there are two really distinct groups of patients. These life-threatening young kids, I think they can continue to be treated with extended access program for the time being while we get some more confirmatory data. It looks like there are not clinically catastrophic effects in the more adult population. The benefits are mostly related to quality of life, functional capacity, 6-minute walk test, and that's where all the uncertainty is; and that if you were to do another study, it doesn't seem to me like you will be putting those patients' lives at risk; that in 3 months, 6 months, you can get some data.

I would love to have the FDA be flexible, but the flexibility is not necessarily to approve a drug based on data for which there are so many uncertainties out there. I would rather have the flexibility of a second trial with some Bayesian borrowing from the first data, or not having a Frequentist, a stringent, p-value of 0.05, or some other way of flexibility of getting the data.

If there are already more than 90 percent of the patients that are being followed, then if the benefits are profound, doing a small RCT for a few months seems to me will be feasible, especially considering that we're talking about giving a drug for the rest of the patient's life for which there are so many uncertainties. I think you will not jeopardize the young kids who will continue to get the extended access program in relatively short term. Again, I'm not at all underestimating that it's really hard work to do, but still in a relatively modest time frame, we can get a more definitive answer.

I will just make one final comment. Sorry. Also, if in the randomized-controlled trial, even if the p-values were not there, but even if there was a trend -- because the cardiolipin ratios did improve by 12 weeks, if there were trends, but then subsequently they became statistically significant, that's a different story. But we really did not see any trend in any of the secondary endpoints. Thank you.

Dr. O'Connor?

DR. O'CONNOR: Thank you. Chris O'Connor, and I want to thank everyone for a great discussion, and thoughtful. I want to make, really, three points. One is that we have a different mindset when evaluating efficacy evidence for ultra-rare disease, and I think that's been articulated nicely. The three components that went into my decision were that the randomized-controlled trial was partially discounted, in in my mind, because of the behavior of the placebo patients.

Number two, I think 201, Part 2, and 001, for me, because there was a large effect size across multiple domains of large effect size, I think the probability of all that happening is not random. Even though 60 percent of that effect size may have occurred early, there was still enough effect size late that met and exceeded the estimands of what the sponsor had predicted. So that overcomes, I think, the biases of being non-random of the placebo effect. The third point,

which we haven't talked much about, is the benefit-risk, and I think that the safety profile of this is very good, so the benefit risk ratio for me is very favorable.

DR. BUTLER: Dr. Alexander?

DR. ALEXANDER: You know, these advisory meetings are never held when the issues are black and white, and they're always really informative as well. I don't think regulatory flexibility gets you beyond the paucity of affirmative evidence in this setting. There's the absence of key affirmative mechanistic data, so if the FDA's report is to be believed, there's no data on the effect of the drug on apoptosis or necrosis, and then there's not just no data, but no improvement in the drug on cardiac function. There was a completely negative well-controlled trial, and then there were rapid and large effects within 12 weeks of transition to an open-label design.

So I guess what guided my vote -- and I think you said, or I should say that I voted no -- was that the externally-controlled trial

isn't adequate and well controlled for the reasons that have been well specified, not just the nature of the outcome, but the risk of bias and the issues with imputation. We only spent one slide on it, I think, but just consider this 64-week outcome example where, if I understood correctly, the FDA said that the mean difference in days, from 64 weeks when that was assessed in the natural cohort, was a year, a year before and a year after what was characterized as a 64-week outcome.

So I think that it makes good sense to take a totality of evidence approach, and this is a threshold matter, and I certainly understand and believe that the FDA should tolerate more residual uncertainty than for diabetes or heart failure, but I just don't think that this is a setting where that would get you across the line.

I guess I'm also still stuck with this randomized withdrawal design and whether or not there's enough power, and how many people it would take, and this question about how quick the washout period is. But I certainly think that's one

appealing design to be probed further, depending upon what happens with the development program. Thank you.

DR. BUTLER: Thank you.

Dr. Shaw?

DR. SHAW: Hi. Pamela Shaw, and I also voted no. I think Dr. Butler and Dr. Alexander really expressed very well a lot of the reasons that I had. I 100 percent agree with your concerns. In particular, I focused on the word, "can you conclude" that this drug is effective, and I can't. I'm very compelled by the case study evidence, thinking that could be supportive to a well-controlled study, which we don't have, and that's fundamentally to me the issue.

I wish we had better mechanistic data. So either there needs to be existing data brought forward or new studies could be done. I think that could add to the totality of evidence. I think if there are at least some patients -- we're not looking for a gold standard clinical trial -- who could be studied, maybe in a crossover fashion

where each person is their own control, I think that would be tremendous use of gathering more systematic evidence because if we approve this trial, our ability to understand what's going on is going to go out the window because we won't be able to do anymore systematic studies.

I have a huge concern. This is a very vulnerable population. I'd be afraid to approve a drug with the lack of systematic evidence that we currently have. The case studies that are coming forward are really compelling, so can we do something with these new upcoming compassionate use cases, or even going back -- most universities and many organizations have electronic health records. Can we get any data from the experience on this drug to add to the table? I think we haven't maximized the analysis.

Finally, I would really urge for any future studies; that we really need to up the rigor of the analysis. And when we have a long term follow-up study where we're only looking at 8 out of the original 12, we need to go and think about those

other four so we have a better idea of understanding if this swing-up is just from selection bias. So I would hope, even with the existing data, there'd be some more to learn to increase the rigor of the data we already have.

DR. BUTLER: Thank you.

Dr. LePichon?

DR. LePICHON: So this was an agonizing decision for me. I spend most of my time, if not all of my time, working with children with progressive neurological diseases and neurodegenerative diseases, and I face those parents every day. Usually I'm in the room with them saying, "Damn FDA," and in this case, I'm on the other side of the table, and that made this decision incredibly difficult.

In making this decision, it went against every single instinct that I have to advocate on behalf of the patients. Making it even harder, several of the people I admire and respect actually gave some impressive testimony as to how good this drug is, so that made it even harder for me to come

to this decision.

But I was asked, is this an adequate and well-controlled investigation, and is the confirmatory evidence sufficient to support that elamipretide is effective? So if I looked at each step, the randomized-controlled study, I don't think that there is anything more that we need to say about it; it was a negative result. The single arm, there's so much phenotypic heterogeneity, I don't understand how those conclusions can be used. We have nothing to compare to. Furthermore, we're looking at a time when the kids are relatively stable, the kids and adults I should say.

The natural history, I just was mind-boggled, and I'm not a statistician, but this issue of the propensity scores and the imputed values just left me dumbfounded. Because of this, I did not feel comfortable trusting any of the data on the natural history. So in the end, even though I was incredibly impressed by the case reports, I could not in good conscience say that I felt convinced that elamipretide was an effective drug.

DR. BUTLER: Thank you.

Dr. Jonsson-Funk?

DR. JONSSON-FUNK: Yes. There's no shortage of uncertainty here, and I think everybody has shared that. That said, when I tried to think about what information could feasibly be acquired that would resolve that uncertainty, I found it very hard to come up with anything that I think is going to be sufficiently clarifying that it will remove the uncertainty that we have right now. And so I'm left with a reasonably good chance that this is an effective drug, at least in some group of people, based on very imperfect data and analyses, but where I believe the magnitude of the effect that we saw was large enough to overcome the most serious of those concerns for my part.

I think the other question of type 1 versus type 2 error is really important to think about here; what are the harms of calling this ineffective if it actually is? And given the lack of what I see as a feasible path forward to getting definitive evidence, I voted yes.

DR. BUTLER: Thank you.

Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. I want to start by thanking the Barth community, the sponsor, and all of the others working on finding a treatment for this disease. This was obviously extremely difficult, but I voted no on the question in front of me. The available evidence supporting the effectiveness is, unfortunately, not conclusive, even with somewhat relaxed standards.

The concerns raised by FDA regarding selection bias, residual confounding, and limitations of effort-dependent endpoints are all valid and substantial; however, the data presented does by no means allow conclusion of an absence of benefit, so much of the data in front of us are very compelling. With that, in the context of a disease as rare as Barth syndrome, I'm still not sure what that should mean for the approval decision, given the difficulties in generating meaningful additional data in the foreseeable future and the large proportion of patients that

are on the drug.

It's really an ethical question or a philosophical question; what if you had a hypothetical drug for an otherwise untreatable rare disease with a 50 percent probability of effectiveness that is reasonably safe, for which you will not likely get better data and that has no current alternatives? I think we're pretty close to this scenario. All that said, if you'd asked me about drug approval, I likely would have voted yes based on the same argument that Dr. Jonsson-Funk has just made.

As to recommendations for additional data, I think all options seem problematic. A potentially longer controlled trial may be helpful, however, it will be logistically challenging and factually unblinded given the injection site reactions present; therefore not addressing one of the primary concerns. A withdrawal study could be another approach but would suffer from the same limitations, and I think we'd be more likely than not, after an additional trial was conducted, to

find ourselves in the exact same situation that we're in now. Thanks.

DR. BUTLER: Thank you very much.

Dr. Kishnani?

DR. KISHNANI: I just wanted to really thank the community and the sponsor, really, for putting all this information together. Having seen patients with Barth syndrome, I know what the clinical course can look like and also working in the rare disease space, but I have to say this has been one of the most difficult decisions for me that I've made today, and I could easily be swayed the other direction.

Just telling me that these data were not completely compelling, it really did not meet the criteria for an AWC. As I even mentioned during the discussion, there was not a good natural history study; it was almost like a convenient sample. However, the patient testimonies were remarkable, the forest plots all going in one direction was helpful, and whilst in the open-label component, the maximum benefit in that first

12 weeks, the fact that it was maintained was kind of helpful to me.

But yet what I feel in this rare disease space is there are significant gaps, and when we have patients on expanded access, we have the limitation because the data collected are just so limited and sparse. We have to find a way to get more of this information so that it can be more clinically meaningful and allow us to make better decisions. And here, this approval, if it were to go forward, I would still hope that the label would be very carefully written so that it leaves room, and for the sponsor to continue to do some studies in the pediatric population, or in those under 12, which could then guide us in the future.

So all in all, as a clinician, as I said, I got swayed to say it as a yes, but I could easily be swayed the other way. The data were not the greatest.

DR. BUTLER: Thank you.

Ms. Shuman?

MS. SHUMAN: Hi. Yes. This is Devin Shuman

speaking. I'm not sure what I can say going last that has not been said before, but I will echo a lot of the concerns people have. I think, for me, it ended up landing on the side of the fence of could I reasonably conclude that this is effective based on the data that is available or would become available for a syndrome such as Barth and the difficulties around trying to measure mitochondrial disease, and I landed on the side of I think that you can very reasonably conclude that caveat.

Is it accelerated access or something else? I will leave that to the FDA, especially when you take this safety profile into consideration as well, which I know we weren't technically supposed to, but I feel like no one's really brought that up too much at the end here. I think, for me, I do feel confident that it's a reasonable conclusion to come to based on the evidence we have and that we will be able or unable to get through further studies.

DR. BUTLER: Great.

Well, thank you very much. I appreciate

everybody's vote and perspective. My apologies that we ran a little over time, but the discussion was robust. I would really like to thank all the panel members for all their insightful questions, comments, and their erudite input to the discussion. I would also like to thank all the open presenters, public hearing presenters and the public, and also thank the both the presenters from the sponsor and from the FDA, and thank the FDA for convening this meeting. Thank you very much.

Before we adjourn, are there any final comments from the FDA?

DR. JOFFE: I think you said it all. I want to thank you all for carefully considering the data and providing your recommendations. Of course, we'll take this all back internally and discuss further, and decide what our final decision will be. I also want to thank all the patients and the caregivers who came here today and shared very personal difficult parts about their lives courageously, and we appreciate you taking the time to come speak. Thank you to the sponsor as well,

and that's it for me.

Adjournment

DR. BUTLER: Thank you. The meeting is adjourned.

(Whereupon, at 5:45 p.m., the meeting was adjourned.)