FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE (PCNS)

Tuesday, November 24, 2015

8:04 a.m. to 5:31 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Philip A. Bautista, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEMBERS (Voting)

G. Caleb Alexander, MD, MS

(Chairperson)

Associate Professor of Epidemiology and Medicine

Johns Hopkins School of Public Health

Center for Drug Safety and Effectiveness

Baltimore, Maryland

Emilia Bagiella, PhD

Professor of Biostatistics

Department of Health Evidence and Policy

Mount Sinai School of Medicine

Icahn Medical Institute

New York, New York

Nicole R. Gonzales, MD

Associate Professor

University of Texas-Houston Medical School

Department of Neurology - Stoke Program

Houston, Texas

Richard P. Hoffmann, PharmD

(Consumer Representative)

Drug Information Consultant/ Medical Writer

Hernando, Florida

Michelle M. Mielke, PhD

Associate Professor

Division of Epidemiology

Department of Health Sciences Research

Mayo Clinic

Rochester, Minnesota

Chiadi U. Onyike, MD

Associate Professor of Psychiatry and

Behavioral sciences

Division of Geriatric Psychiatry and

Neuropsychiatry

Department of Psychiatry and Behavioral Sciences

The Johns Hopkins University School of Medicine

Baltimore, Maryland

Bruce I. Ovbiagele, MD, MSc, MAS

Professor and Chairman of Neurology

Medical University of South Carolina

Charleston, South Carolina

Justin A. Zivin, MD

Professor Emeritus

Department of Neurosciences

University of California, San Diego

Co-Founder, Integrated Deficit Examinations, LLC

Rancho Santa Fe, California

TEMPORARY MEMBERS (Voting)

Christopher Cassidy

(Patient Representative)

Annandale, Virginia

Michelle M. Estrella, MD, MHS

Attending Nephrologist

Bayview Medical Center and Johns Hopkins Hospital

Associate Faculty member at the Welch Center for Prevention, Epidemiology, and Clinical Research

Baltimore, Maryland

A. Reghan Foley, MD

Staff Clinician

Neuromuscular and Neurogenetic Disorders of Childhood Section, Neurogenetics Branch

Division of Intramural Research

National Institute of Neurological Disorders of Stroke (NINDS)

National Institutes of Health (NIH)

Bethesda, Maryland

Mark W. Green, MD, FAAN

Professor of Neurology, Anesthesiology, and
Rehabilitation Medicine
Director of Headache and Pain Medicine
Icahn School of Medicine at Mt Sinai
New York, New York

Cheri Gunvalson, RN, MS

(Patient Representative)
Clinical Assistant Professor
University of North Dakota, College of Nursing
Grand Forks, North Dakota

Rodney L. Levine, MD, PhD

Chief
Section on Protein Function in Disease
Laboratory of Biochemistry
National Heart, Lung, and Blood Institute, NIH
Bethesda, Maryland

Aaron S. Kesselheim, MD, JD, MPH
Associate Professor of Medicine
Harvard Medical School
Director, Program on Regulation, Therapeutics, and Law (PORTAL)
Division of Pharmacoepidemiology and Pharmacoeconomics
Brigham & Women's Hospital
Boston, Massachusetts

Glen Nuckolls, PhD
Program Director and Executive Secretary
Interagency Muscular Dystrophy Coordinating Committee, Neurogenetics Cluster
Division of Extramural Research
NINDS, NIH
Bethesda, Maryland

Paul Romitti, PhD

Professor

Department of Epidemiology and Interdisciplinary

Program in Toxicology

University of Iowa

Iowa City, Iowa

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Mark Gordon, MD

(Acting Industry Representative)

Director, Clinical Development and Medical Affairs

General Medicine/Central Nervous Systems

Boehringer Ingelheim Pharmaceuticals

Ridgefield, Connecticut

FDA PARTICIPANTS (Non-Voting)

Ellis Unger, MD

Director

Office of Drug Evaluation I (ODE I)

Office of New Drugs (OND), CDER, FDA

Robert Temple, MD

Deputy Director

ODE I, OND, CDER, FDA

Billy Dunn, MD

Director

Division of Neurology Products (DNP)

ODE I, OND, CDER, FDA

Eric Bastings, MD

Deputy Director

DNP, ODE I, OND, CDER, FDA

Ronald Farkas, MD, PhD

Clinical Team Leader

DNP, ODE I, OND, 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

(8:04 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you haven't already done so. I'd also like to identify the FDA press contact, Sandy Walsh. If you're present, can you please stand? Thank you, Sandy.

My name is Dr. Caleb Alexander, and I'm the chairperson of the Peripheral and Central Nervous System Drugs Advisory Committee meeting. I'll now call this meeting to order. We'll start by going around the table and introducing ourselves. Let's start down here on the right, please.

DR. GORDON: Good morning. My name is Mark Gordon from Boehringer Ingelheim. I am the industry representative.

DR. ESTRELLA: Good morning. I'm Michelle Estrella from Johns Hopkins University. I'm a nephrologist.

DR. FOLEY: Good morning. My name is Reghan Foley. I'm a staff clinician working at the NIH.

DR. NUCKOLLS: Hi. I'm Glen Nuckolls. I'm the program director for the muscular dystrophies at the National Institute of Neurological Disorders and Stroke.

DR. LEVINE: I'm Rod Levine. I'm at the National Institutes of Health. I'm a neonatologist and a biochemist.

MS. GUNVALSON: Hi. I'm Cheri Gunvalson. I'm a nurse. I'm on faculty at the University of North Dakota, and I have a son who's 24 with Duchenne.

DR. HOFFMANN: I'm Richard Hoffmann. I'm a pharmacist and medical writer, and I'm on this committee as the consumer representative.

DR. GREEN: I'm Mark Green. I'm a professor of neurology at Mount Sinai School of Medicine and director of headache and pain medicine.

DR. GONZALES: Good morning. Nicole Gonzales. I'm a neurologist at the University of Texas Medical School in Houston.

DR. BAUTISTA: Good morning. My name is Phil Bautista. I'm the DFO for this committee.

DR. ALEXANDER: I'm Caleb Alexander. I'm a general internist and pharmacoepidemiologist at Johns Hopkins.

DR. OVIBAGELE: Good morning. I'm Bruce Ovbiagele, a neurologist at the Medical University of South Carolina.

DR. ZIVIN: Justin Zivin, professor emeritus, University of California San Diego. My area of specialty was stroke.

DR. BAGIELLA: Emilia Bagiella. I'm a biostatistician from the Mount Sinai School of Medicine.

DR. MIELKE: Michelle Mielke. I'm the department of epidemiology and neurology at the Mayo Clinic.

DR. KESSELHEIM: Good morning. My name is Aaron Kesselheim. I'm an internist, lawyer, and health policy researcher in the division of pharmacoepidemiology and pharmacoeconomics at Brigham and Women's Hospital and Harvard Medical

School.

DR. ROMITTI: I'm Paul Romitti. I'm a professor of epidemiology and toxicology at the University of Iowa, and also direct our statewide Iowa registry for congenital and inherited disorders.

DR. FARKAS: Ron Farkas. I'm a clinical team leader in the Division of Neurology Products at FDA.

DR. BASTINGS: Eric Bastings, deputy director of the Division of Neurology Products at the FDA.

DR. DUNN: My name is Billy Dunn. I'm the director of the Division of Neurology Products.

DR. UNGER: I'm Ellis Unger. I'm the director of Office of Drug Evaluation I at FDA.

DR. ALEXANDER: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that

individuals can express their views without interruption.

Thus, as 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 topics during breaks or during lunch. Thank you.

Now, I'll pass it to Phil Bautista, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. BAUTISTA: The FDA is convening today's meeting of the PCNS under the authority of FACA of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, 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 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that the members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC 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 particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 USC 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 NDA 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Incorporated, for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping, as determined by genetic testing.

This is a particular matters meeting, during

which specific matters related to BioMarin's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by 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 may have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Mark Gordon is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by Boehringer Ingelheim Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or 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. ALEXANDER: Thank you. We'll now proceed with the FDA's introductory remarks from Dr. Billy Dunn, director of the Division of Neurology Products.

FDA Introductory Remarks - Billy Dunn

DR. DUNN: Thank you, Dr. Alexander. I prepared some brief comments for the committee and for the audience before we get to the meat of the discussion. I'll try to keep them brief; we have a lot to cover today.

Good morning to you all and welcome to all our committee members, to our guests who have traveled here, and to all the folks who are joining us by electronic means for this very important

meeting. I want to thank the committee for your willingness to be here, your eagerness to consider the important topics we will discuss today, and your forthrightness in sharing with us your perspectives on the application under consideration.

I want to especially thank the public attendees, both in person and those who are joining us by audio or video broadcast, for their commitment to finding a treatment for Duchenne muscular dystrophy. I particularly want to note and thank the patients with DMD who are joining us today. Your efforts to be here are invaluable and tremendously appreciated. Thank you.

On a broader note than just this committee meeting today, I want to take a moment to mention how much we here at FDA appreciate our interaction with the DMD community. We have been very engaged with the scientific and advocacy leaders in this area, which I am confident has resulted in an improved understanding for both the community and ourselves.

The tireless efforts of the DMD community resulted in a proposed draft guidance from an advocacy group that was submitted to us for our consideration. I'm happy to say, building on that effort, we published our own draft guidance in June of this year for DMD.

We are here to discuss drisapersen for the treatment of Duchenne muscular dystrophy in patients with mutations amenable to exon 51 skipping. There is without question a profound unmet medical need in DMD. We have no approved treatments for this serious disease. We are highly sensitive here at the agency to the urgency needed for the development of an approved therapy for DMD.

Before briefly describing some of the issues we will ask you to discuss today, I want to stress to you that we have not made any final decisions on the approvability of this application. The information in your background packages are primary reviews only that do not yet take into account today's proceedings.

The primary reviewers were asked to submit

clear recommendations on approvability in their reviews, but those recommendations should be viewed as just that, recommendations. They should not be viewed as the opinion or conclusion of anyone other than the author of the individual review.

The reason we are here today is to gain your input into some of challenging issues we have confronted during our review process so that we may incorporate it into our ultimate decision on approvability.

As will be discussed in detail during the presentations you will hear today, drisapersen is theorized to lead to clinical benefit by potentially increasing the production of a truncated form of dystrophin. The natural form of dystrophin, a key muscle protein, is profoundly deficient in DMD, and the gene defect giving rise to this deficiency is thought to be the primary underlying cause of the disease.

How much of this truncated dystrophin drisapersen is designed to produce could be helpful remains an open question. Of possible relevance to

this question is the fact that some patients with DMD have very small amounts of a naturally occurring truncated dystrophin that does not appear to be associated with an appreciable slowing of muscle degeneration; and some patients with a related form of muscular dystrophy, Becker muscular dystrophy, naturally produce the same truncated dystrophin that drisapersen is designed to produce and have only mild disease. In these Becker patients, the truncated dystrophin is present at levels of 50 to 100 percent of what normal dystrophin would be.

The sponsor conducted biomarker studies to assess whether dystrophin was actually increased by drisapersen, and clinical studies to assess whether drisapersen conferred a clinical benefit. The clinical studies included three randomized clinical trials of interpretable design, including a large phase 3 study that did not show an effect on its primary efficacy outcome and two somewhat smaller phase 2 studies.

These studies have been reviewed in great

detail by our staff, and key points will be presented to you today by several members of our primary review staff: Dr. Veneeta Tandon, a clinical reviewer in the Division of Neurology Products, who will discuss efficacy findings; Dr. Sharon Yan, a statistical reviewer in the Office of Biostatistics, who will discuss statistical issues; Dr. Ash Rao, a reviewer in the Office of Biotechnology Products, who will discuss dystrophin methodologies and supporting assay validation, and Dr. Evelyn Mentari, a safety reviewer in the Division of Neurology Products, who will discuss safety considerations.

These presentations will highlight a number of issues, including intra-study inconsistencies in the phase 2 studies and inter-study inconsistencies between the phase 2 studies and the phase 3 and biomarker studies, along with an examination of the safety findings associated with the use of drisapersen.

We have provided discussion topics and questions to help frame your discussion following

the presentations. First, we ask the committee to discuss the strength of efficacy evidence for drisapersen in the first phase 2 study, a study with a positive drisapersen arm, with particular attention to the inconsistency of results when compared to the other drisapersen arm and to the lack of statistical significance on secondary endpoints, which might have been supportive.

Next, we ask the committee to discuss the strength of efficacy evidence for drisapersen in the second phase 2 study, with particular attention to the lack of statistical significance on the primary outcome measure in the high-dose group, to the inconsistency of results when compared to the low-dose group, and to the lack of support from secondary endpoints in that trial.

Then, we ask you to discuss what impact the lack of statistical significance in the primary outcome measure of the large phase 3 study, along with a lack of support from its secondary endpoints, has on the persuasiveness of the phase 2 trials themselves.

Additionally, we ask you to discuss the evidence provided on drisapersen and dystrophin production and the impact of that evidence on the interpretation of the clinical results.

Finally, we will ask you to discuss the overall strengths and weaknesses of the drisapersen efficacy data and the acceptability of its safety profile.

These are complicated issues, and we will be asking you to vote on several questions and will be listening very carefully to your discussion of all these topics. The content of your discussion is of great importance to us.

Again, I stress that no final decision has been made on approvability, and we very much look forward to the insights you will provide. We have convened this committee because we feel that a final decision requires your input and advice. Thank you for the substantial efforts you have made in preparing for and attending this meeting, and thank you for the important work you will do today.

Dr. Alexander, thank you for the time to

offer my comments, and I return the proceedings to you.

DR. ALEXANDER: Thank you.

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, 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 BioMarin Pharmaceutical's presentations.

Sponsor Presentation - Camilla Simpson

MS. SIMPSON: Dr. Alexander, members of the committee, FDA staff, good morning. My name is Camilla Simpson, and I am global head of regulatory affairs and pharmacovigilance at BioMarin. On behalf of BioMarin, thank you for your time today to consider our proposed therapy, drisapersen, for the treatment of Duchenne muscular dystrophy, a universally fatal, rare, progressive neuromuscular disorder.

Drisapersen represents the first new therapeutic option in almost 30 years for Duchenne patients in the United States. The development program began with Prosensa in 2006. From 2009 through 2014, Prosensa partnered with GSK. When that partnership dissolved, all patient treatment was suspended.

In January 2015, BioMarin acquired Prosensa and all rights to this product. Today is a culmination of the work of many employees, investigators, global health authorities, patients, and their families.

We also recognize the patient advocacy community, which has driven, supported, and partnered with companies and the FDA, developing the FDA guidance on Duchenne muscular dystrophy, an unprecedented achievement, and who have been pioneers for patients with this disorder when there was no industry presence.

With drisapersen, we at BioMarin continue our commitment to developing novel treatments for patients around the world suffering from rare genetic diseases. Based on our analysis, which is rooted in our expertise in rare disease treatments, we have confidence that drisapersen, as part of a comprehensive care program, is a viable therapeutic choice for Duchenne patients and their families.

Duchenne results from mutations, usually catastrophic deletions, in the gene coding for the

protein dystrophin, which is essential for normal muscular activity. When there is an out-of-frame deletion, such as a common exon 45 to 50 deletion, this results in the loss of production of functional dystrophin.

Drisapersen is a modified antisense oligonucleotide with a sequence optimized to skip exon 51, which restores the reading frame for the dystrophin messenger RNA and results in production of a shortened functional dystrophin protein.

The proposed indication for drisapersen is for the treatment of Duchenne with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping, as determined by genetic testing. Drisapersen is formulated for subcutaneous administration at a weekly dose of 6 milligrams per kilogram of body weight.

In our quest for a new therapeutic option for Duchenne patients, we have found it to be an enormously challenging disorder to study due to its rarity, heterogeneity, and rapid progression.

Limited natural history was available at the

start of the program to guide the design, a global clinical program that has been conducted in 326 patients in over 70 clinical trials across 5 continents. In the context of rare disease, this program, in terms of participants, is equivalent to studying 65 percent of all eligible U.S. patients.

Three randomized, placebo-controlled studies were conducted in parallel due to the urgent medical need of Duchenne patients. One was clearly positive. One was strongly supportive. Consistent results were observed in the third study in comparable patients. The safety profile of drisapersen is well characterized and acceptable in the context of treating a universally fatal disorder.

It turns out to be the rule, rather than the exception in rare diseases, that regulatory flexibility needs to extend from early phases of development to the design of adequate and well-controlled studies required to demonstrate effectiveness and safety to support marketing approval.

FDA has historically and consistently employed considerable, yet reasonable, flexibility in interpreting and in applying statutory requirements for effectiveness and safety for persons suffering from rare diseases.

BioMarin has made a long-term commitment to the Duchenne community to systematically gather additional information to further understand drisapersen's effects. Specifically, our plans include a post-approval registry to holistically long-term outcomes; a post-approval risk management plan tailored to guide safe and appropriate use of drisapersen; additional post-approval clinical studies to evaluate drisapersen in subsets of Duchenne patients not yet studied.

These comprehensive plans will help to secure the real-world use of drisapersen as a safe and effective treatment option for patients and families devastated by this disorder.

Our presentation begins with Dr. McDonald from University of California at Davis. He will detail the pathophysiology and natural history. He

will discuss the particular complexities of designing and conducting clinical trials in Duchenne.

Dr. Fuchs will then review the clinical efficacy results from the development program, integrating the full scope of study results to provide the most complete picture of drisapersen's effectiveness.

Dr. Campion will follow with her review of safety data, showing the safety is well characterized. He will also review our comprehensive risk management plan and post-approval activities.

Dr. McDonald will then provide a benefit-risk assessment based on the pattern of results that support drisapersen for the treatment of Duchenne. Dr. Fuchs will return with concluding remarks.

In addition to Dr. McDonald, we have invited the following experts to join with us to respond to your questions: Dr. Kathryn Wagner and Dr. Nathalie Goemans, both neurologists specializing in

Duchenne; Dr. Kari Connolly, a dermatologist; Dr. Tim Goodnough, a hematologist; and Dr. Anthony Portale, a pediatric nephrologist.

Now, to provide the perspective on the complexities of studying Duchenne, here is Dr. Craig McDonald from UC Davis.

Sponsor Presentation - Craig McDonald

DR. MCDONALD: Good morning. Thank you for the opportunity to provide you with an overview of the natural history and clinical trial challenges for Duchenne muscular dystrophy. My name is Craig McDonald. I hold the position of professor of physical medicine and rehabilitation in pediatrics at the University of California at Davis, and I'm the director of the neuromuscular disease clinics there. I've received compensation as a consultant for BioMarin. I have no financial interest in the outcome of today's proceedings.

I've been involved in the treatment of over 800 patients with Duchenne over the past 25 years. I've been a principal investigator on several industry-sponsored clinical trials for Duchenne

conducted by various companies and have directed the Cooperative International Neuromuscular Research Group, CINRG, Duchenne natural history study, funded by the federal government and patient organizations.

Duchenne muscular dystrophy is caused by a lack of dystrophin, an essential muscle cell protein responsible for shock absorption and protection of the muscle cell from load-induced damage and also cell signaling. It is not a contractile protein responsible for strength or force generation. Deficiency of dystrophin causes damage to the muscle cell membrane, leading to a progressive loss of muscle fibers.

At the early stages of the disorder, there's a competition between contraction-induced muscle damage and the regenerative capacity from localized stem cells, as well as from normal growth and maturation.

On the left is an H&E stain of normal muscle fibers in an unaffected boy. The lack of dystrophin in Duchenne muscles leads to shearing of

muscle cell membrane and causes cellular damage and muscle fiber loss.

On the right, we observe the end stage of Duchenne, with few scattered muscle fibers and a significant replacement of fibers by fat and fibrotic scar tissue. Eventually, a critical threshold of loss of skeletal muscle fibers is reached, leading to a precipitous loss of function in a heterogeneous manner.

The hallmark of Duchenne is progressive muscle weakness, which severely impacts physical function at a young age. Skeletal muscle weakness impairs early motor development in infancy; acquisition of gross motor milestones; ability to rise from the floor, exemplified by the Gowers sign; ability to climb stairs; and impaired walking ability.

Muscle weakness-related immobility leads to joint contractures and scoliosis, often requiring the need for splinting or surgical intervention. In the later stages of the disorder, weakness of the respiratory muscles leads to need for

mechanical cough-assist devices and ventilator support.

Initial subclinical myocardial impairment is followed by profound ventricular dilatation and dysfunction in the later stages of the disease. The main cause of death in most patients is due to cardiac or respiratory failure. Despite current care, the mean age of survival is in the mid to late 20s.

Here we show the important and mostly irreversible milestones of loss of ability to stand up, loss of ambulation, loss of self-feeding, and requirement of respiratory assistance. Although early loss of one functional milestone leads to early onset of the next milestone, there is a wide variability in the time frame in which these sequential losses occur.

This heterogeneity is linked to many factors, including genetic factors, physiological factors such as maturation and baseline muscle function, and external factors such as medical management and differences in standard of care.

Despite the publication of management guidelines in 2010, the current management of Duchenne is variable between clinics, and more so between different countries. Glucocorticoid use has impacted motor and respiratory function. Physical therapy and splinting helps to prevent contractures.

The more aggressive management of pulmonary and cardiac impairment, as well as scoliosis surgery has improved overall survival. However, these treatments are not curative, and in the past 30 years, treatment options have not changed significantly. To date, no product has received FDA approval for the treatment of Duchenne.

Time-to-function tests are the most often-used tests to assess functional ability in Duchenne patients. The reasonably well-maintained ability to perform most functional tasks despite obvious motor dysfunction in these patients is demonstrated in the following video.

(Video played.)

DR. MCDONALD: Here we see a boy, 9 years

and 9 months old, prior to the enrollment in a clinical trial for drisapersen. His rise from floor is 7 seconds, about two to three times the time needed for an age-matched control. His 6-minute walk distance is 414 meters, about 60 percent of his predicted 6-minute walk distance.

So here you can see he's using the Gowers maneuver as a compensatory strategy to stand from the floor. He's unable to sit from a seated position without the use of his upper arms. He's unable to jump. He's unable to hop. Many Duchenne patients never develop the ability to hop on one leg. You can see his obvious impairment in gait despite a well-preserved 6-minute walk distance. And he has difficult with the one-step stair ascent and stair descent.

In the following video, we see a boy at the age of 9 who in 2007 was one of the first Duchenne patients to perform a 6-minute walk test as part of the original validation of the functional tool in Duchenne. His 6-minute walk distance was 330 meters. You can observe his rise from floor, which

is compromised at 13 seconds, but he has a reasonable reserve capacity of muscle strength and uses a compensatory strategy to perform the task.

Here we see the same young man at age 17. We observe the catastrophic progression of Duchenne. Despite supportive treatment, the disorder has progressed over 8 years, leading to an inability to transfer between the bed and chair and perform even the most basic activities of daily living. His father is assisting him from the bed to the chair and back.

You can observe his significant contractures at the knee and at the ankle. And at night, he requires respiratory assistance due to weakness of the diaphragm. This relentless progression of disease is what I have seen in almost all my patients with Duchenne.

There are distinct challenges in studying Duchenne in the context of controlled clinical trials. There are no primary and secondary endpoints that can be appropriately applied across the entire spectrum of Duchenne patients, and in

fact, even across all ambulatory patients. The rare and heterogeneous nature of this population make this a particularly difficult population to study.

An obvious biomarker to explore disease status is dystrophin. This was the subject of a large FDA workshop in March of this year. While progress is being made, it was concluded that the field is still evolving with regard to the methods of measurement and interpretation of quantitative results.

Dystrophin levels are difficult to interpret due to sampling issues, background noise of the signal, and the wide variability in the quality of muscle biopsies. Furthermore, it was the consensus that there was no clear relationship between dystrophin levels and physical function. Dystrophin measurements are useful in detecting pharmacological activity of disease-modifying intervention. However, limitation in the use of this as a surrogate biomarker exists.

The 6-minute walk test has been used as the

primary efficacy endpoint in registration trials for at least 11 approved products in other diseases, as indicated in the table on the left.

Our group at the University of California at Davis performed the original work on the validation of the 6-minute walk test as a measure of endurance in walking function in Duchenne beginning in 2007. Since that time, the 6-minute walk test has been a commonly-used primary endpoint in ambulatory Duchenne trials. In addition, the 6-minute walk distance is prognostic for future walking ability.

It is essential to view the changes in the 6-minute walk test in relationship to patient-reported outcomes. The Peds QL is an often-used patient-reported outcome tool. On the left, we can observe the relative insensitivity of this measure in Duchenne patients when compared to unaffected controls vis-a-vis the 6-minute walk distance.

Recently, more sensitive tools have been employed to address this. The Pediatric Outcome Data Collection Instrument, or the PODCI, patient-reported outcome scale has been used and validated

in a variety of musculoskeletal disorders.

On the right, we see the close relationship between the 6-minute walk distance and the PODCI transfer basic mobility patient-reported outcome measure in Duchenne. Longitudinal data shows the correlation between the 1-year changes in the 6-minute walk distance, and the PODCI is highly correlated with an R value of 0.93.

More importantly, our group has shown that even small improvements of less than 20 meters in Duchenne patients with limited ambulation are still anchored to clinically meaningful changes in this patient-reported outcome measure.

Recent insight in the natural history has revealed the heterogeneous trajectory of functional loss in Duchenne patients. In this figure we see the longitudinal data in 107 patients, showing their variable trajectories of the 6-minute walk distance.

At young ages, while Duchenne patients have reduced function in comparison to healthy boys, most patients are still increasing their walking

ability. However, when the 6-minute walk distance falls below about 300 meters, we observe a rapid but heterogeneous drop in walking ability.

In addition to the challenges of heterogeneity, ambulatory exon 51 skipping amenable Duchenne patients are extremely rare. Clinical investigators must contend with the challenge of finding patients who meet eligibility criteria.

Of the 2300 patients estimated to be able to benefit from exon 51 skipping treatment, only about 1,000 are able to ambulate without the need of any assist device. For the purposes of performing a clinical trial with the 6-minute walk test as a primary endpoint, probably only half, or about 500, of these patients would qualify to participate.

With the constraints and time limitations of any clinical program, as well as the great heterogeneity in this rare population, this is a very difficult disorder to study. It is therefore also of great importance to extract as much data as possible from these trials in this ultra-rare patient population.

The knowledge of Duchenne is constantly evolving, and therefore we should interpret the outcomes of clinical trials through the lens of the natural history data available at the time these trials were designed. This change of increasing understanding of the disorder can be seen in the development programs for the treatment of Duchenne.

While the 6-minute walk test has continued to be a primary endpoint, there has been a significant shift in the inclusion criteria of Duchenne trials over the last 5 years, as shown in this graph. Patients with lower 6-minute walk distance, less than 300 meters, and greater heterogeneity of progression have been excluded from ambulatory Duchenne trials.

In addition, patients with higher baseline ambulatory function have also been excluded in 48-week trials because they don't tend to change much for their ambulatory endpoints. Furthermore, more narrow subpopulations are now often included as prespecified subgroups.

Duchenne muscular dystrophy is a devastating

and relentlessly progressive disorder that's incredibly difficult to study. There remains an urgent need for an improved treatment that will benefit patients.

Next, Dr. Fuchs will describe how the drisapersen program addressed these challenges.

Sponsor Presentation - Henry Fuchs

DR. FUCHS: Good morning. My name is Hank Fuchs, and I will be presenting the efficacy from the drisapersen clinical program.

Drisapersen is a breakthrough therapy. Advancing treatment for rare disease requires rigor in balancing biologic and statistical evidence. During today's deliberation, it is the aggregation of evidence that most wisely informs our judgment.

This presentation will provide an overview of the clinical program and a summary of the pharmacological activity of drisapersen. Baseline characteristics of the study populations will be presented, followed by the results from three randomized, placebo-controlled studies and two long-term studies. I will close with summary

remarks and conclusions. We begin with an overview of the development program.

The drisapersen program is the first new drug application submitted to the FDA and the first to be reviewed by an advisory committee for Duchenne muscular dystrophy. The efficacy studies are listed here by study number, study design, and number of patients.

The initial study, PRO051-01, showed exon 51 skipping and dystrophin production following a single local, intramuscular injection in four patients. Study PRO051-02 demonstrated the safety of subcutaneous administration. It also suggested the biologic activity of systemically administered drisapersen.

At that stage, three randomized, placebo-controlled studies were initiated called studies 117, 876, and 044. For clarity, these studies will be referred to hereafter as studies 1, 2, and 3. The long-term safety and efficacy study 349 enrolled patients exiting studies 1 and 3.

It's important to see this program in its

historical context. Preclinical and early clinical work occurred from 2006 to 2009, supporting proof of principle by demonstrating the presence of exon skipping dystrophin production and dose identification in phase 1 studies.

Results from these studies were published in the New England Journal of Medicine. Encouraging results from the initial proof of concept and dose-finding studies, along with the severe nature of the unmet medical need, led to the implementation of a large program with three randomized, placebo-controlled studies that ran concurrently.

These studies provided three independent estimates of effect. Because of this parallel approach, there was no opportunity to use the results of one study to inform the next, but the totality of the results informs our understanding of the benefits of therapy. Importantly, key natural history publications were not available until nearly the end of the program.

To recruit the number of patients necessary for all of these studies, sites around the world

were utilized. Study 1 was a randomized, double-blind, placebo-controlled study that enrolled 53 patients from 13 centers in 9 European countries and Australia.

The primary objective of study 1 was to assess the efficacy of continuous or intermittent subcutaneous dosing of drisapersen versus placebo administered over 24 weeks. Efficacy over 48 weeks was the secondary objective of the study. After screening and randomization, there was a 3-week loading dose. Importantly, this is the only study in which a loading dose was used.

Study 2 was a randomized, double-blind, placebo-controlled, dose-ranging study that enrolled 51 patients from 13 centers in the United States. The primary objective of study 2 was to assess the efficacy of drisapersen versus placebo administered over 24 weeks. Efficacy measures were also assessed at week 48. After screening and baseline randomization, there was a 24-week dosing period followed by a 24-week post-treatment period when patients were not dosed.

Study 3 was the largest randomized, double-blind, placebo-controlled study and enrolled 186 patients from 44 centers in 19 countries outside of the United States. Many of the centers involved had not participated in study 1 and were selected based on prior participation in clinical trials and not because of their expertise in Duchenne.

The primary objective of study 3 was to assess the efficacy of drisapersen versus placebo administered over 48 weeks. After screening and baseline randomization, there was a 48-week dosing period followed by follow-up enrollment into an extension study.

Across the entire clinical development program, 326 patients were enrolled at more than 70 trial sites in 25 countries on 5 continents.

The pharmacology of drisapersen was evaluated as part of the randomized studies and supports the proposed dose regimen and route of administration. Here we see the results from study 3, in which no loading dose was administered. This figure shows that steady-state tissue

concentrations of drisapersen are not approached until 36 weeks.

Dystrophin expression has been demonstrated and found to be tissue concentration-dependent. Results are presented here from study 1, in which the highest quality biopsies were available. This study also used a 3-week loading dose.

These results show that above a tissue concentration of 10 micrograms per gram of tissue, dystrophin expression is increased. Below this concentration, there were limited increases in dystrophin. Putting these data together allows us to form an understanding of the relationship between drug tissue concentration and pharmacologic outcome.

In study 1 with a loading dose, tissue concentrations, which drive drisapersen expression are achieved. In spite of the loading dose, after intermittent administration, tissue concentrations are at the margin to drive dystrophin expression.

In study 2, tissue concentrations are achieved, but because of the long half-life of

drisapersen and dystrophin, dystrophin levels continue to build while off treatment.

In study 3, partly because of the lack of the loading dose and also because of advanced muscle impairment, critical tissue concentrations are lower and dystrophin production lags. Acknowledging that these are not normalizing levels of dystrophin, we do see a consistent pattern of effect. Importantly, this pattern will be expanded after I review the efficacy results.

Next, we'll look at inclusion criteria and baseline characteristics of the three randomized, placebo-controlled trials, which are listed here.

The key inclusion criteria were similar for studies 1 and 2. They required patients to be ambulant, age 5 years or older, have an exon 51 skippable mutation, be on stable glucocorticoids prior to screening, have a baseline 6-minute walk of at least 75 meters, and have a rise from the floor time of less than or equal to 7 seconds.

Critically, the only study that didn't have those criteria was study 3. It omitted rise from

floor criterion, which meant that the functional status of these patients was determined only by the baseline 6-minute walk distance of at least 75 meters.

At the time of the study design, available literature suggested that that level of functioning would be adequate to ensure that all patients remained ambulant through the course of the 48-week study. We now know that that was an incorrect assumption, which resulted in the inclusion of patients whose ambulatory function was going to decline aggressively and whose residual lower extremity muscle mass was insufficient to demonstrate benefit during 48 weeks of therapy.

As a result of the eligibility criteria differences, patient populations in studies 1 and 2 differed from study 3, as shown in baseline demographic characteristics. Study 1 and study 2 were very similar in terms of age, baseline 6-minute walk, and rise from floor.

Study 3 included a more severely affected patient population. The age range of enrolled

patients was greater, there was nearly a 70-meter difference in terms of the baseline 6-minute walk, and a more than twofold increase in the baseline rise from floor, from 5 seconds in studies 1 and 2 to 13 seconds in study 3, with 13 percent of individuals unable to perform that function.

Next, we will consider the results of the three randomized, placebo-controlled studies, with a focus on the proposed dose of 6 mgs per kg per week.

A standardized functional endurance measure, the 6-minute walk distance test, was selected as the primary endpoint for all three studies and has been used to study many other diseases. Six-minute walk distance in patient-reported outcomes correlate with well-being, both cross-sectionally and longitudinally. These data also suggest that even a small change in 6-minute walk distance are meaningful at lower levels of baseline walk.

The test measures improvements in mobility and endurance but doesn't capture changes in other aspects of the disease. Therefore, additional

endpoints were selected to assess other challenges that patients face.

It was understood that significant treatment effects may not be achieved for these endpoints during the trial. Notably, time function tests were also used in clinical trials of glucocorticoids earlier in Duchenne patients.

Several study quality measures were implemented. The result of these efforts was high quality data with few missing data points. Rigorous blinding was maintained through the use of a matching placebo, separation of caregiver and assessor, implementation of standardized training program for endpoint evaluation, videotaping of 6-minute walk distance tests for quality control, and no communication of results from ongoing studies were shared with sites or with patients.

This is the primary endpoint result from study 1. In study 1, the 6-minute walk distance for the drisapersen arm increased from baseline by 32 meters compared with a 4-meter decline in the placebo arm. This resulted in a 35-meter treatment

difference at week 24 in favor of drisapersen, with a p-value of 0.014. There were no discontinuations, and all patients were included in the intent-to-treat analysis.

This is the result for study 1 displayed as a cumulative distribution function plot depicting all data without statistical modeling. The X-axis represents change from baseline at week 24 in the 6-minute walk, and the Y-axis shows the percentage of patients who had at least that level of change for any given value. The curve shows a treatment advantage for drisapersen, with the drisapersen curve shifted to the right of the placebo curve.

In this plot, we see that 44 percent of placebo patients showed an increase in walking distance compared to 72 percent of drisapersen-treated patients.

Several ambulatory function tests were measured as secondary endpoints, and the results are presented here as a forest plot. There was a positive trend in all of these measures in favor of drisapersen.

Interestingly, the magnitude of these changes are comparable to those observed in the original studies that led to the use of corticosteroids as a standard of care in the treatment of patients with Duchenne. The treatment effects represented here are additive to those standard of care.

A trend for improvement on quality of life as measured by the Peds QL was also observed for the drisapersen group for both child and caregiver reports, with mean treatment benefits for both. This result is particularly impressive in light of the relative insensitivity of this measure in Duchenne patients.

Turning now to study 2, a similar result for the primary endpoint was seen as with study 1. The drisapersen arm increased from baseline by 16 meters compared with an 11-meter decline in the placebo arm, resulting in a 25-meter treatment difference at week 24 in favor of drisapersen, with a p-value of 0.069. There were no discontinuations, and all patients were included in

the intention-to-treat analysis.

Here we see the cumulative distribution function plot for study 2. As with study 1, the curve shows a treatment advantage for drisapersen, with the drisapersen curve shifted to the right of the placebo curve. We see that 56 percent of placebo patients showed an increase in walking distance compared to 72 percent of drisapersen-treated patients.

The results from several ambulatory function tests are presented here as a forest plot. Some but not all measures showed a trend in favor of drisapersen, likely due to the delay in achieving critical tissue concentrations by week 24 due in part to the absence of a loading dose. However, as a secondary endpoint, study 2 used a functional outcomes survey to document family and caregiver observations in the changes in the ability of the patient to perform usual day-to-day activities.

Here we see the proportion of patients who had an improvement within a given domain of functional outcome by treatment group. The three

domains were mobility, physical activities, and hand dexterity. A consistent trend in favor of drisapersen is seen across all three domains.

Presented here is the primary endpoint result from study 3. In contrast to studies 1 and 2, both arms in study 3 showed a reduction in the 6-minute walk distance, with a more modest treatment effect of 10 meters at week 48 in favor of drisapersen with a p-value of 0.415, likely as a result of the lack of loading dose and the inclusion of patients who are more progressed at baseline. Four individuals in the treatment arm discontinued, one in the placebo arm. All patients were included in the intention-to-treat analysis.

Given the encouraging results from studies 1 and 2, we were surprised and initially puzzled by the study 3 results. This is the corresponding cumulative distribution function plot for study 3. I want to highlight a couple of characteristics that give us insight into the result.

One is that, as anticipated from the broadened inclusion criteria, this study had a high

proportion of individuals who experienced accelerated decline. Nearly a quarter of patients had a decline in walking distance of 100 meters or more during the 48-week study period. When you bear in mind that natural history data tell us to anticipate a decline of 40 to 60 meters per year, we can see that there were a number of severely affected patients in the study.

A second characteristic is that from the point of decline of 100 meters or less, that is, moving to the right on the plot, the curves separate in favor of drisapersen. For example, in terms of patients having any increase in walking distance, this level of improvement is seen in 24 percent of placebo patients compared to 37 percent of drisapersen patients.

The results from several ambulatory function tests are presented here as a forest plot. As in study 2, some but not all measures showed a trend in favor of drisapersen, and as in study 2, this study lacked a loading dose.

Study 3 also included the clinical global

impression of improvement scale, which provides a physician's holistic assessment of the benefit of treatment. These values are based on rating the status of the patient compared to baseline.

There is substantial effect in favor of drisapersen in terms of the overall clinician assessment of how these patients have fared. The bars on the left side of the chart show that 30 percent of drisapersen-treated patients improved compared with just 5 percent of patients on placebo.

In light of the evidence found in study 3, we sought to evaluate benefit in comparable populations across studies. To do this, we investigated the combined data from the three studies, which I will now summarize.

To construct comparable populations, we used predictive baseline characteristics. The baseline characteristics of the entire study population across the three placebo-controlled studies were examined to identify a group of patients whose baseline 6-minute walk distances were comparable.

The entire range for baseline 6-minute walk distance is shown here on the blue banner. The 48-week treatment estimates for subgroups were calculated for 6-minute walk distance, shown here in brackets, to enable evaluation between comparable populations.

For further analysis, we selected the middle of this range across the pooled population. This approach removes the most severely affected and the least severely affected patients from the analysis, and includes a sufficient sample size between treatment groups to enable interpretation.

Each patient's baseline 6-minute walk distance is plotted here to show how each study contributes to this analysis. The size of each bubble represents the number of patients at each point. In total, 76 drisapersen patients and 52 placebo patients contributed to the analysis, according to baseline 6-minute walk distance. Approximately half of each study's patient population is included.

Using this comparable group of patients, the

treatment effect was analyzed in the pooled study populations and by each study individually.

Here we see the results according to baseline 6-minute walk distance. These analyses show that improvement in 6-minute walk distance observed in the subgroup of study 3 is similar in both direction and approximate magnitude to the pooled data, with overlapping confidence intervals. We acknowledge that the results of each study are not identical.

This result is true for study populations defined by another important predictive factor, baseline rise from floor. As with baseline walk, these analyses show that improvement observed in the pooled population is similar to what is observed in study 3 in both direction and magnitude. Importantly, the consistency of benefit between studies is even more apparent. This is significant in light of the change in eligibility based on the rise from floor parameter for study 3.

Some interpretive caveats bear important mention.

First, this approach is not intended to suggest that a post hoc analysis of a subgroup of study 3 provides stand-alone, statistically robust evidence of a treatment benefit. The intention is to demonstrate that the strong findings of studies 1 and 2 are in fact substantiated by relatively similar findings across comparable populations.

Second, identifying this more responsive population does not imply that there is a lack of benefit for the remaining population. The aim is to demonstrate simply that study 3 does not negate the findings of studies 1 and 2.

Secondary endpoints for study 3 were also explored using the subgroup of patients, the results of which show a similar pattern of consistency with the results observed in studies 1 and 2, with five ambulatory function tests showing a trend in favor of drisapersen. Here we see the results for the population defined by baseline walk.

We believe the primary efficacy findings in the aggregate provide substantial evidence of

effectiveness. There is a consistent shift in favor of drisapersen in three independently conducted trials, strengthening the persuasiveness of each individual study result.

Study 3 shows consistent benefit of drisapersen in comparable groups of patients, as seen in studies 1 and 2, and variability of results among the trials can be explained. In addition, these three placebo-controlled studies provide evidence from a number of secondary endpoints measuring ambulatory function and quality of life, offering further support for drisapersen.

We'll now look at the long-term extension study. Study 349 examined the long-term safety and efficacy of studies 1 and 3. As a reminder, all patients received drisapersen treatment during this extension study.

This figure summarizes the treatment effect observed in the extension phases of studies 1 and 3. Study 1 results displayed represent summary statistics for 6-minute walk distance change from baseline between the 6 mg per kg per week

continuous dose group and placebo.

The first column, in blue, shows the treatment difference of drisapersen versus placebo at week 48 in study 1. The second column, in purple, shows the difference between patients who received 2 years of treatment compared to patients who received 1 year of treatment in the extension study.

In study 1, the separation between treatment arms observed at week 48 is slightly increased to 50 meters at week 96. In study 3, the separation between treatment arms observed at week 48 is extended to 30 meters by week 96. Results in the delayed treatment groups, those who received placebo in the controlled phase of the study, reinforce the need to treat early to maintain functional capacity.

With continued treatment in this extension study, a positive trend in favor of drisapersen is seen in the ambulatory function secondary endpoints, shown here as a forest plot. In addition, improvement in muscle biomarkers were

observed, with significant decreases in creatinine kinase and lactate dehydrogenase, both of which are indicators associated with muscle damage. What these figures also show is a treatment response in those patients previously treated with placebo as they transition to active treatment at week 48.

Having completed a thorough review of the clinical outcomes, I want to return to the pharmacology data that I presented previously to put the main clinical findings in the proper context.

The first observation that I would like to make puts clinical outcomes in the context of drisapersen tissue concentrations that have been achieved. In less severely progressed patients in studies 1 and 2, concentrations shown on the X-axis correlate with improvements in 6-minute walk distance on the Y-axis. However, in the more progressed patient population enrolled in study 3, increased tissue concentrations are associated with stabilization of disease progression.

Recall the integrated pharmacology model

relating concentrations to dystrophin expression measured in our randomized trials. In this model, faster delivery of drisapersen to tissue results in better dystrophin expression.

Now, let's overlay the clinical benefit observed in the same trials. First, the best clinical outcomes in the program are observed in the study with the loading dose. The next best results are observed from weekly administration in study 2 without a loading dose and maintained due to the long tissue half-life of drisapersen in dystrophin expression in spite of cessation of treatment.

Importantly, intermittent cycles, which did not result in benefit at week 24 presumably due to two previous cycles off therapy, eventually do manifest treatment benefit as tissue concentrations accumulate.

Because of the low delivery of drisapersen to the tissue of patients with more progressed disease, treatment benefit is modest in study 3, but with time results in more impressive

improvements in 6-minute walk distance. Finally, absence of treatment benefit is observed when lower doses are administered.

Next, we'll look at the long-term follow-up study, study 673. This was an extension study of the original phase 1 dose-finding study. Of the 12 patients, one was non-ambulant from the beginning, and another was not able to complete the 6-minute walk test at the entrance to the extension study, so this chart depicts the 10 ambulant patients.

It shows the 6-minute walk tests at baseline and then subsequently over time in weeks below on the X-axis. Despite the advanced age of a number of patients, there is remarkable stability over 3 and a half years of treatment.

The two individuals who did lose ambulation were individuals who had the lowest baseline function, below 330 meters. When we compared these results with untreated natural history controls matched by age, 6-minute walk, and steroid treatment, we found that of the 9 patients with

matches, 7 performed better than their match controls and no patients performed worse. Importantly, no 673 patients with a baseline 6-minute walking distance of greater than 330 meters lost ambulation versus 25 percent of natural history controls.

Our conclusions from the analysis of the study data are:

Substantial evidence of effectiveness has been established. This is based on three randomized, placebo-controlled studies with a relevant clinical primary endpoint, the 6-minute walk distance test. Consistent, important effects are seen across all randomized, placebo-controlled studies and are influenced by population differences and the use of a loading dose, and influenced by regimen.

Treating a younger patient population when muscle function is still relatively well-preserved affords a better opportunity to stabilize or improve function with a shorter duration of treatment. When treatment is started in older and

more progressed patients, not only is the overall effect more likely to be a slower decline rather than stability or improvement, but the duration of treatment needed to see a more robust treatment effect is greater.

Evidence from a number of secondary endpoints measuring ambulatory function and quality of life offer further support for drisapersen. There's a durable benefit evident for more than 3 years after the start of therapy.

Thank you very much. Dr. Giles Campion will now present an overview of drisapersen safety.

Sponsor Presentation - Giles Campion

DR. CAMPION: Thank you and good morning.

The safety of drisapersen was evaluated in 9 clinical studies of Duchenne patients comprising more than 500 patient-years of exposure. The data indicate that drisapersen has an acceptable and manageable safety profile, and overall, we are in agreement with the safety conclusions reached by the FDA.

My presentation will cover the following

topics. I will begin by reviewing the extent of patient exposure, followed by an overview of adverse events, serious adverse events, and discontinuations in both placebo-controlled and open-label extension studies. Then I will describe adverse events of special interest. I will finish with postmarketing risk mitigation plans for drisapersen, including monitoring recommendations and educational activities.

The safety of drisapersen has been evaluated in the largest integrated database of Duchenne patients assembled to date. At the time of the NDA submission, a total of 285 patients between the ages of 5 and 16 years were treated with drisapersen for periods ranging up to 3.6 years. More than 200 patients were treated for at least 1 year, and 122 received at least 2 years of treatment. At the 120-day safety update, 297 patients had been treated with drisapersen, corresponding to more than 500 patient-years of exposure, and no new safety findings were identified.

A comprehensive safety monitoring plan was followed in all drisapersen clinical studies. In addition to standard clinical trial safety assessments, adverse events of special interest were pre-identified based on nonclinical experience and published safety data for other phosphorothioate oligonucleotides and specifically monitored.

Adverse events of special interest comprised thrombocytopenia, renal abnormalities, injection site reactions, inflammation events, coagulation abnormalities, and hepatic abnormalities.

Drisapersen was generally well tolerated in placebo-controlled studies. Nearly all patients in both the placebo and drisapersen-treated groups experienced at least one adverse event. The incidence of mild and moderate adverse events was similar for both groups, and the incidence of serious adverse events higher for drisapersen.

There were no deaths in the program, and importantly, the incidence of serious adverse events was similar in both groups. Two patients

treated with drisapersen experienced adverse events resulting in treatment discontinuation, and these will be detailed later in the presentation.

The most common adverse drug reactions, defined as adverse events with at least 5 percent incidence and at least twice the placebo rate, are shown in this table. Injection site reactions, subclinical renal laboratory abnormalities, and arthralgia were the most commonly reported adverse reactions.

I will now summarize the safety data and repeat-dose studies from both placebo-controlled and long-term extension studies, beginning with serious adverse events.

A total of 55 patients, 9 on placebo and 46 on drisapersen, experienced at least one serious adverse event. When adjusted for exposure, the incidence rates were similar in the placebo and drisapersen-treated patients.

The 46 drisapersen-treated patients experienced 66 serious adverse events. Thrombocytopenia was the most common serious

adverse event, reported in 8 patients. Other important treatment-related serious adverse events that will be discussed later in the presentation were one report of glomerulonephritis and one report of nephrotic range proteinuria.

In repeat-dose studies, 12 patients reported adverse events that led to permanent treatment discontinuation. Thrombocytopenia was the only adverse event that led to treatment discontinuation in more than one patient.

Single patients discontinued treatment due to renal events of glomerulonephritis or nephrotic range proteinuria, and a single patient discontinued treatment due to an injection site reaction in repeat-dose studies of up to 3.6 years of treatment.

With respect to adverse events of special interest, more patients treated with drisapersen than placebo experienced injection site reactions and renal abnormalities. Information events, consisting primarily of fever and laboratory markers of information, were similar in the two

treatment groups.

Coagulation abnormalities were more frequent with placebo. Hepatic abnormalities were infrequent in both groups, but slightly higher with drisapersen. These were primarily asymptomatic laboratory findings of mild to moderate increases of glutamate dehydrogenase and gamma glutamyl transferase.

There were no reports of thrombocytopenia in the placebo-controlled studies of up to 48 weeks of treatment. However, thrombocytopenia events were reported in the extension studies after longer exposure and as summarized in the next slide.

Across all repeat-dose studies, 20 patients experienced thrombocytopenia events. Most events were mild to moderate asymptomatic decreases in platelet count that were either subclinical or result with treatment interruption.

Eight patients had serious adverse events with platelet counts less than 50, the range being between 5 and 35. None of these patients had a clinically significant bleeding events. Six

patients had counts of less than 20, and most had minor clinical symptoms such as epistaxis.

The time to onset from the start of drisapersen treatment a count below 20 was below 14 to 26 months. Five patients had anti-platelet antibodies at the time of the event. All 8 patients recovered, with counts returning to more than 75 within a medium time of 3 weeks and a range of 1 to 9 weeks after discontinuation of treatment, and there were no re-challenges.

I will now summarize our updated risk mitigation plan for thrombocytopenia, which is in line with the FDA's recommendations.

Our risk mitigation plan for thrombocytopenia includes caregiver and healthcare provider education on recognizing signs and symptoms of thrombocytopenia and close platelet count monitoring. Platelet counts should be measured at baseline and every 2 weeks, with an immediate platelet count if clinical signs or symptoms of thrombocytopenia develop.

Treatment should be interrupted and anti-

platelet antibody testing performed if platelet counts fall below 75. Dosing may be resumed based on individual benefit/risk assessment after recovery of counts to 150 or more. Treatment should be permanently discontinued if platelet counts fall below 50 or if anti-platelet antibody testing is positive.

I will now discuss the renal abnormalities that were observed in the drisapersen clinical trials.

Across all studies involving over 500 patient-years of exposure, 2 patients experienced clinically significant renal events considered possibly related to drisapersen treatment. These both involved nephrotic range proteinuria, identified by urine monitoring -- one event of glomerulonephritis, confirmed by renal biopsy, and one event of nephrotic range proteinuria without a renal biopsy. These events are likely to be immune-related, and both resolved with treatment discontinuation.

Monitoring demonstrated that hematuria was

sporadic, not progressive, and not associated with other renal events. Occasional serum cystatin C increases were modest and not progressive. The vast majority of renal events were subclinical, nonprogressive, low molecular weight proteinuria such as alpha-1-microglobulin, which will be discussed further in the next slide.

Our clinical program implemented a highly conservative approach to renal monitoring that included precautionary treatment interruptions for confirmed levels of proteinuria of trace or more. As a result of this effort, we learned that clinically significant renal abnormalities were in fact rare.

In approximately 78 percent of patients receiving drisapersen in repeat-dose studies, treatment was interrupted due to finding of trace or more protein on spot urine protein quantification. However, this slide shows that in 86 percent of cases, measurement of a 24-hour urine protein was in the normal range, less than 300 milligrams per day, and drisapersen treatment could

be restarted. In only 4 percent of patients did abnormal proteinuria recur, and it too was reversible.

Only two of these patients, less than 1 percent, had nephrotic range proteinuria, which resolved after permanent treatment discontinuation. Therefore, although the incidence of proteinuria adverse events was high in repeat-dose studies as a result of the strict screening criteria, the true incidence of protein on the 24-hour urine collection was low, at 14 percent.

Proteinuria was predominately low molecular weight and thought to represent interference with tubular reabsorption by drisapersen rather than tubular injury. These findings allowed us to develop an appropriate risk mitigation plan to ensure detection and management of potential renal injury.

This plan, developed in collaboration with external experts, is similar to what was required in clinical trials and will include quantitative urine protein and serum cystatin C monitoring.

Urine protein will be monitored at baseline at every 2 weeks; 24-hour urine protein testing will be initiated if there are two consecutive values greater than or equal to 50 milligrams per deciliter, or a single value of greater than or equal to 200 milligrams per deciliter.

Treatment will be interrupted if 24-hour values exceed 300 milligrams per meter squared. Treatment will be resumed if 24-hour values drop below 250 milligrams per meter squared, or a random urine protein drops below 50 milligrams per deciliter. Treatment will be discontinued if 24-hour values exceed 1 gram per meter squared.

Serum cystatin C will be monitored at baseline and monthly. Treatment will be interrupted if values increase above 50 percent of baseline. When values return to baseline or the normal range, treatment can be resumed.

Injection site reactions were the most common adverse event associated with drisapersen treatment. Two patients had serious events of injection site edema. Most reactions were reported

as mild to moderate. Severe reactions occurred in 9 patients treated with drisapersen at 6 milligrams per kilogram per week. One patient in the program discontinued treatment due to the reaction, which was injection site edema.

Common or significant events included injection site erythema, discoloration, induration, pain, and atrophy. The mean duration for injection site reactions was 58 days, with 21 percent of injection site reactions reported as not recovered or resolved at the end of the study. With long-term treatment, injection site reactions may progress and become dose-limiting. They may also continue to progress after stopping medication.

A disproportionate number of dermatologically significant injection site reactions were reported in extension study 673. The 12 boys in the study who received up to 3.6 years of treatment had a period a subcutaneous administration of drisapersen exclusively in the abdomen for the first 50 to 72 weeks of weekly treatment. This may have contributed to the

development of more dermatologically significant injection site reactions and led to the requirement to rotate injection sites.

Shown on the slide are representative photographs of the more pronounced injection site reactions that may occur. Generally, the first symptom to occur is erythema, shown in the upper left panel, typically with an onset within the first month of treatment.

As sites are used more frequently for injection, the next symptom is often discoloration, followed by induration, atrophy, and in rare cases, sclerosis and ulceration at the site of sclerotic skin due to scratching or mechanical abrasion. The true incidence of late onset injection site reactions may be higher, as not all patients have been treated for the same extended duration.

Our risk mitigation plan for injection site reactions will include a requirement that drisapersen should be administered by healthcare professionals, prescribing information and educational material with detailed instructions for

proper injection technique, and strict rotation of injection sites, recommendation for annual dermatological assessments with additional consultations as needed for patients with persistent injection site reactions, and ongoing study of intravenous dosing as an alternative to subcutaneous administration.

Systemic inflammation did not emerge as a clinically relevant safety issue. In the ambulant placebo-controlled studies, 30 percent of patients treated with drisapersen and 27 percent with placebo reported an inflammation adverse event.

No inflammation adverse event led to withdrawal from treatment, and one patient had an inflammation serious adverse event of grade 2 pyrexia. In aggregate, inflammation biomarkers in the ambulant placebo-controlled studies were within the normal range or abnormal shifts were not clinically relevant.

Single case reports were viewed for evidence of drug-related systemic inflammation. These include myocarditis, myocardial ischemia, small

bowel obstruction, Henoch-Schonlein light rash, intracranial venous sinus thrombosis. In these cases, no consistent pattern in the affected or in the systems was seen, and some events resolved with ongoing treatment or did not recur with continued therapy.

BioMarin is committed to a comprehensive postmarketing program to further characterize the safety profile of drisapersen, protect patients, and broaden knowledge to inform benefit-risk decisions. Our program will include a registry to evaluate long-term safety and efficacy outcomes, a risk mitigation plan to guide safe and appropriate use of drisapersen that includes rigorous monitoring, a medication guide, education for healthcare providers, caregivers, and patients, and enhanced pharmacovigilance to further quantify and characterize known and potential risks, and additional clinical studies to evaluate drisapersen in a subset of Duchenne patients not yet studied, including patients under 5 years of age and patients who are non-ambulatory. Further study of

IV administration of drisapersen as an alternative to subcutaneous administration is also planned.

In summary, the safety of drisapersen was evaluated in the largest database of Duchenne patients assembled to date. Key drug-related safety findings were injection site reactions, infrequent severe thrombocytopenia, and rare glomerulonephritis.

Identified and potential risks are manageable through close monitoring and risk mitigation measures, which will be included in the prescribing information.

Our postmarketing surveillance program will further refine understanding of the known and potential risks of drisapersen. With these measures in place, patients and their families can be confident that drisapersen treatment can be well managed in the context of this catastrophic disorder. Thank you.

Dr. Craig McDonald will now present a benefit-risk assessment of drisapersen based on the clinical trial results.

Sponsor Presentation - Craig McDonald

DR. MCDONALD: Thank you. Duchenne is a debilitating and devastating disorder in children, and there is precious little available to treat them. We have a responsibility to make this therapy available to patients in light of the benefits and risks that I'll now review.

The drisapersen program included the largest cohort of Duchenne patients ever studied in placebo-controlled trials to assess a disease-modifying treatment. This is a challenging patient population to study. It is rare and highly heterogeneous.

Despite these difficulties, the sponsor has demonstrated consistent and positive outcomes on ambulatory function in three placebo-controlled trials that were conducted simultaneously. Quality of life improvements were also apparent.

To put the drisapersen results in an even greater context, I'd like to refer to the findings of the effects of glucocorticoids on Duchenne because the favorable trend seen in the rise from

floor in study 1 are reminiscent of the findings we observed in the early days of implementing glucocorticoids as a supportive treatment in Duchenne.

The Cochrane review on glucocorticoid use in Duchenne demonstrated an improvement of 2.7 seconds in the rise from floor over 6 months. Although initially just a signal, we now know that over the long term, this has led to significant prolonged ability to climb stairs and ambulate, prolonged time to self-feed, delayed time to ventilator use, and prolonged survival.

I have personally observed these benefits of glucocorticoids and have published these data based on the CINRG Duchenne Natural History Study. The data today shows that continuing glucocorticoids and adding drisapersen for one year improves the rise from floor by another 2.9 seconds.

While prolonging milestones cannot be captured in a 48-week trial of drisapersen, it is nonetheless encouraging to see improvement in rise from floor and 6-minute walk distance in study 1.

I look forward to realizing these kinds of benefits over the next several years as longer-term use of drisapersen ensues.

In my professional opinion as a physician qualified by scientific training with extensive experience in Duchenne, I can fairly and responsibly conclude that drisapersen provides meaningful treatment benefits to patients.

The safety profile of drisapersen has been well characterized through an extensive clinical program. As a clinician, I am confident that based on the extensive experience gained in this clinical program, treating physicians will understand what the risks are and provide patients and caregivers sufficient information to make an informed decision on whether to use drisapersen.

Furthermore, physicians will know how to monitor patients and manage these risks. Therefore, it is my scientific conclusion that the benefits of treatment with drisapersen outweigh the risks.

My thoughts regarding the safety and

effectiveness of drisapersen is further informed by my personal clinical experience in treating 10 patients within the clinical trial program. This is one of my patients, shown at almost 9 and a half years of age. He participated in study 3 in Canada and was started on the drug at 5 years of age.

Despite an initial loss of 58 meters in the first 48 weeks of study 3, likely due to the delay in delivery of drug to muscle, he has subsequently gained 130 meters versus baseline after 3.6 years of total treatment.

(Video played.)

In the next video, you will see an unprecedented maintenance of physical function for Duchenne. He can perform his clinical tests with a remarkable maintenance of functional ability, arising with no Gowers sign. He can stand from a chair without the use of his upper extremities. He can jump. Unlike many Duchenne patients who never develop this ability, he can hop on one leg.

He can actually perform the 25-meter run

test, running with both feet off the ground in a near-normal fashion. He can even run uphill. I have never seen a nearly 10-year-old Duchenne patient achieve this level of functioning.

My experience with individual clinical study patients, along with my understanding of the overall clinical trial results presented today, give me great hope for Duchenne patients who may have the opportunity to be treated with this drug. The benefits of drisapersen clearly outweigh the risks. There are perhaps even greater risks to not make drisapersen available to Duchenne patients who could benefit.

I look forward to the discussion today and would be happy to answer any questions you may have regarding my experience with treating Duchenne patients and my perspective on the encouraging results of the program. Thank you.

Sponsor Presentation - Henry Fuchs

DR. FUCHS: With respect to the persuasiveness of the overall clinical program, the totality of data provides substantial evidence of

effectiveness and safety of drisapersen in patients amenable to exon 51 skipping. Duchenne is an enormously challenging disorder to study. It is extremely rare, heterogeneous, and rapidly progressive.

Limited natural history data was available at the start of the program. We acknowledge the issues highlighted in the questions posed to the committee. However, in spite of these issues, there are dimensions of strength of evidence that must also be considered.

We demonstrated persuasive evidence of effect in three randomized, placebo-controlled studies with a relevant clinical primary endpoint, the 6-minute walk test. The pattern of trial results across these studies demonstrates consistent shifts in favor of drisapersen. Proper understanding of consistency of effect in comparable populations further strengthen the persuasiveness of the clinical data.

The exploration of different dosing regimens strengthen our confidence in the proposed dose of

6 mgs per kilo per week and highlights the importance of a loading dose. Our understanding of the time to tissue distribution and the critical importance of the relationship between tissue concentration, dystrophin synthesis, and clinical outcome increases this confidence.

The committee must also consider the pattern of evidence across the entire program, one that includes disease context, biology, pharmacology, and trial results. Through our extensive clinical program, we have identified the important side effects and we know how to help physicians manage them. Our perspective is that this evidence supports an overall conclusion that drisapersen represents a safe and effective option for patients.

We as the sponsor are committed to the Duchenne committee, as we are with other rare diseases we target, through post-approval registry, risk management plans, and clinical studies in subpopulations not yet studied.

A big decision is at hand, and it's

important for the committee to help all of us stay focused on the big picture. We believe that adequate information is available now to inform physicians to prescribe drisapersen for Duchenne patients. And with that, our team would be privileged to take any questions the committee has. Thank you.

DR. ALEXANDER: Thank you very much. I'd like to thank the sponsor for their presentation.

Before we move to clarifying questions for the sponsor, I just wanted to ask for Chris Cassidy and Dr. Onyike, if you'd like to briefly introduce yourselves, as well as Dr. Temple, who's joined us.

MR. CASSIDY: Hi. I'm Christopher Cassidy. I'm the patient representative on the advisory committee. And I'm proud to be the first individual with Duchenne muscular dystrophy to actually serve as patient representative. So thank you.

DR. ONYIKE: I'm Chiadu Onyike. I'm associate professor of psychiatry at Johns Hopkins University School of Medicine, where I direct the

young onset dementias program, and focus my work clinically and in research on frontotemporal dementias, which are also orphan diseases. In addition, I also sit on the medical advisory committee of the Association for Frontotemporal Dementias. Thank you.

DR. TEMPLE: Dr. Robert Temple, deputy director of ODE I.

Clarifying Questions

DR. ALEXANDER: Thank you.

Are there any clarifying questions for BioMarin Pharmaceutical? Please remember that all participants from the panel, FDA, and BioMarin should state their name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Hoffman?

DR. HOFFMANN: I was just wondering -- I don't know who would address the question -- but were there any noticeable steroid dose reductions in patients receiving drisapersen?

DR. MCDONALD: Those were evaluated as part

of the trial program. We asked that patients remain on stable glucocorticoid therapy. And we didn't observe meaningful changes in glucocorticoid regimen.

DR. HOFFMANN: Thank you.

DR. ALEXANDER: Dr. Green?

DR. GREEN: I'm not sure who to address this to. But given the relatively narrow therapeutic gain and the prolonged nature of the cutaneous reactions, I was wondering if anyone did a subgroup analysis of those who received these prolonged skin SEs compared to those who didn't.

DR. MCDONALD: I'm going to invite Dr. Goemans up. Dr. Goemans has the longest treatment experience with drisapersen and perhaps the most comprehensive perspective on the program.

DR. GOEMANS: Good morning. My name is Nathalie Goemans. I am a Dutch neurologist and head of the Neuromuscular Reference Center at the University Hospital in Leuven in Belgium. I have been supported for participating in this meeting and have no financial interest in the outcome of

this advisory committee.

I've been treating patients with Duchenne muscular dystrophy for more than 25 years now, and I've conducted several clinical trials in Duchenne muscular dystrophy, including the 673 study, which gives me the longest experience with chronic administration of drisapersen in these children.

I think what I can say about this very long-term study is that, indeed, I have been really surprised by the remarkable preservation of function in these boys over the long term in those that have been started treatment in the stage where we could still preserve ambulation, where we could expect to preserve ambulation. So maybe I can have slide 1 up.

I remind you that this shows the remarkable preservation of ambulation in the cohort of boys that have been treated for more than 3 and a half years. What I would like to point out is that the last point that you can see dates from December 2012.

In the meanwhile, we have a much longer

follow-up of those patients that have been treated continuously since then, with the exception of one year treatment interruption after GSK had decided to interrupt the administration.

So these boys have received an exceeding number of subcutaneous injection. Indeed, we have seen the occurrence of subcutaneous injection, and as have been mentioned before, all patients have been exclusively been injected in the subcutaneous abdomen for quite a long time before this procedure was amended to rotation to other sites.

Because the abdomen was compromised for injection, we were again reduced in our injection site. And we have indeed probably the most severe injection reactions, and I think most of the pictures are indeed from our site.

Saying this and working out the risk and the benefit, I really would like to add and to take this opportunity to say how I've been impressed by the preservation of the function of these boys over time. And as you can notice, the boys that you are seeing now are like 16 to 17 years old. They have

preserved function. They have preserved some of the ability for self-care. They participate with their peers in school trips. Some of them do not even need a wheelchair for longer distances. And in my longer experience with Duchenne muscular dystrophy, this is really unprecedented.

This has been confirmed by the opinion of my colleagues, independent colleagues, that have asked me what treatment I had been giving these boys in consideration of the favorable evolution in these boys.

DR. ALEXANDER: Thank you. I think the question was specifically about whether there were analyses that stratified by the presence or absence of a cutaneous reaction, if I understood the question directly.

DR. MCDONALD: Yes. And we're unable to separate groups of identified patients who have specific vulnerability to skin toxicity and diminished benefit. In general, there's a relatively high frequency of injection site reactions, and I think I took Dr. Goemans' point as

the benefit was substantially larger in her global experience than the risk varied in individual patients.

DR. ALEXANDER: Thank you.

Dr. Mielke?

DR. MIELKE: Thank you. I have a couple questions. One is on slide CE-65. I was wondering, when you look at -- well, study 1, but particularly with study 3, at week 48 you have 176 individuals, and at week 96, 98 individuals.

If you would look at week 48 for those 98 individuals, were they much better performers at that time frame as well? So I'm just wondering if this is more of these individuals were better off to start with, and they continued as well.

DR. MCDONALD: We note the difference in sample size at the two different time points. The principal difference in sample size was the result of the discontinuation of the program by GSK, and therefore, it was relatively stochastic.

We evaluated the completer analysis to see if the results in a completer population were

substantially different from the results that are presented on the slide. If I could have the slide up -- actually, slide 2 up, I should say. This pertains to the right-hand chart, which you were referring to.

So shown on the left side in white are the results from study 3 during the randomized, placebo-controlled trial, ending with approximately a 10-meter difference, as shown on the previous slide, and at the end of week 48, a 30-meter difference.

You can see here, based on the sample size, this is a completer analysis to rule out the possibility of selection bias in the results that we showed. Same result either way.

DR. MIELKE: Okay. I have one other question, if that's okay. The presenters have really highlighted the importance, particularly with slide 1, which had the best effects, with that loading dose.

So my question going forward is your thoughts on -- because you haven't necessarily

proposed the loading dose for approval. But it seems that you're suggesting that that's the best effect that there is. So I'm just curious in terms of your thoughts on that.

DR. MCDONALD: I believe that our package proposal does include a recommendation for a loading dose. If I could have slide 1 up, we can just flash to the recommended dosing regimen, including the loading dose. Because amongst the trials that we've conducted, it does yield the best results among them.

But we also mentioned that we're committed to continuing to study drisapersen and will be investigating further ways to safely drive drisapersen into muscle tissue. And maybe we can do even better than this in a post-approval setting.

DR. ALEXANDER: Thank you.

Dr. Kesselheim?

DR. KESSELHEIM: Hi. I had a question. I noticed that the phase 2 and phase 3 studies, studies 1 and 3, were initiated relatively around

the same time, but then the subsequent phase 2 study was initiated about a year later.

So I was just wondering what the additional hypothesis was that that second phase 2 study was intended to address. And I also noticed that it didn't include the loading dose, and was wondering if there had been information at the time that might have indicated that a loading dose might be useful in that study.

DR. MCDONALD: The results from study 1 to inform the outcome as a result of loading dose were not available at the time to inform the design of the study 2. Study 2 had the benefit of exploring a lower dose.

The agency encouraged the sponsor, and were appreciative that they did, to seek to understand the potential effects of lower doses so that we didn't launch a product at too high a dose. And we're grateful that we've learned, using a clinical outcome variable, that a lower dose is not effective and that you need to use 6 milligrams per kilogram.

DR. ALEXANDER: Thank you.

Dr. Ovbiagele?

DR. OVBIAGELE: Thank you. My question is about the frequency of injection site reactions. Was there a higher frequency in study 1 compared to the others? And within study 1, was there a difference between those who received continuous versus those who received intermittent?

DR. MCDONALD: There does not appear to be a major difference in injection site reactions between the continuous and the intermittent regimens at later time points, at the time point at which you get efficacy.

Interestingly, one of the features of study 2 was the comparison of two different doses on the same schedule, and there was roughly a comparable, at week 24, rate of injection site reactions. So we conclude from this that given the effectiveness of the 6 milligram per kilogram weekly regimen for maintenance, followed by a loading dose, that that's the dose that should be appropriately indicated.

DR. OVBIAGELE: The reason why I asked was just I was wondering about any potential partial unblinding because of the difference with the loading in study 1 versus 2, and a difference in the continuous versus the intermittent.

DR. MCDONALD: Yes. This was an important consideration in the design of the trials from the beginning. I should point out, when the randomized trials were launched, there were no results available on the long-term consequences of drisapersen administration. So there was no expectation at the start of the study.

Additionally, great steps were taken, as per routine in protocols, using 6-minute walk distance. Again, this was one of the main advantages of using the 6-minute walk distance as the primary test. It's been very well studied, and as a consequence, standardized procedures for obtaining the 6-minute walk distance test were employed.

So the site trainers were trained -- I'm sorry. The assessors were separate from the caregivers, who made other clinical assessments.

The people who conducted the 6-minute walk distance test were not provided information about the patient status.

More importantly, the assessors were trained on assessment and coaching of the performance of the test. There were videotapes obtained and reviewed to assure that there was absolutely consistent following of the test procedures.

Finally, no results from ongoing trials were shared, so that any potential long-term information that was being developed wouldn't be shared with clinical trial sites. If you'd like, if there's more follow-up here, we can bring up one of the clinicians to speak about that. But I want to defer to the chair.

DR. ALEXANDER: Thank you.

Ms. Gunvalson?

MS. GUNVALSON: Yes. I have a question about one of the side effects that resulted in a cranial blood clot that resulted in paralysis of the sixth cranial nerve. How would you educate parents and patients to be aware of this or to

highlight it?

In addition, there was a pulmonary embolism. So I'm just curious. How would you go about educating parents of these severe reactions?

DR. MCDONALD: I'm going to ask Dr. Noonberg to come and review some of the clinical data that are relevant to your question.

DR. NOONBERG: My name is Sarah Noonberg. I'm head of clinical development at BioMarin. We looked very closely across our safety database for evidence of thrombotic or thromboembolic events, given the preclinical findings of that, across our database. We only found two events, the venous sinus thrombosis event that you mentioned as well as the pulmonary emboli that occurred in the setting of nephrotic range proteinuria.

So I think that those two cases are very different. The glomerulonephritis with proteinuria is a well-recognized risk factor for clotting events. The venous sinus thrombosis is an unusual case, so we looked very closely for underlying risk factors.

We know that Duchenne is a chronic low-level inflammatory disorder, and that would set the patient up, any patient up, for potential thrombotic events. We did also note that the patient at screening had a markedly elevated CRP of about 22, which is unusual. He actually decreased his CRP during treatment.

We did not find any other important risk factors. And importantly, that patient did not have proteinuria, which would suggest a potential drug effect. So we believe that this is an unusual event. We've looked at it closely. We've consulted experts.

But we don't believe that drisapersen per se increases risk of thrombotic events. The nephrotic range proteinuria in the setting of glomerulonephritis is a separate event, and for that we have monitoring for urinary protein.

MS. GUNVALSON: And has this little boy recovered the paralysis?

DR. NOONBERG: At least follow-up, he did continue to have paralysis of his abducens nerve.

MS. GUNVALSON: Thank you.

DR. ALEXANDER: Thank you very much. There are a number of questions that remain, but we'll have further opportunities for these to be posed.

We'll now take a 15-minute break, and so we will reconvene at 10 minutes after 10:00 a.m. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. Once again, we'll resume at 10 minutes after 10:00. Thank you.

(Whereupon, at 9:55 a.m., a brief recess was taken.)

DR. ALEXANDER: Thank you. We'll resume today's committee, and now proceed with the FDA presentations.

FDA Presentations - Veneeta Tandon

DR. TANDON: Good morning. My name is Veneeta Tandon. I am a clinical reviewer in the Division of Neurology. I will be presenting the FDA efficacy review of drisapersen.

In this presentation, the statistics

reviewer, Dr. Yan from the Division of Biometrics, will discuss her analyses of the efficacy data, and Dr. Rao from the Division of Biotechnology Review and Research will discuss dystrophin assay methodologies used in this application. After their presentation, I will be back again to continue the presentation on the efficacy of drisapersen.

As you heard from the applicant earlier today, the drisapersen program has three randomized, placebo-controlled studies with similar design. I will again point out a few key differences between these studies.

In the top two blue blocks, I highlight the doses evaluated in each study. Study 1, conducted in 53 subjects, evaluated two regimens of the same dose, 6 milligram per kilogram, given either once every week, referred to as the continuous regimen, or given intermittently in a 10-week cycle with twice-weekly and once-weekly doses on alternating weeks and a dosing interruption from the 8th through the 10th week. This will be referred to as

the intermittent regimen in the presentation.

The exposure and total number of doses given by the two regimens were equivalent. Study 2 evaluated two doses, 3 and 6 milligram per kilogram per week. The much larger study 3 evaluated a single 6 milligram per kilogram per week dose. Study 1 included a loading dose of 6 milligram per kilogram, given twice weekly for three weeks. The other two studies did not have a loading dose.

In the blue blocks in the middle of the slide, I point out differences in the study duration and the primary endpoint in each study. Study 1 and 3 were 48-week studies. Study 2 was a 24-week study with a drug-free observation period up to 48 weeks. The primary endpoint was changed from baseline in 6-minute walk distance in all studies, and was assessed at 24 weeks in study 1 and 2 and at 48 weeks in study 3.

The three studies only differed in their inclusion criteria for the rise from floor time. The first two studies included patients with a maximum rise from floor time of up to 7 seconds,

whereas the study 3 had no restrictions on the rise time and enrolled a population that was more impaired at baseline, as shown at the bottom of the slide describing the mean baseline characteristics for the three key prognostic factors, rise time, age, and 6-minute walking distance.

The study 3 patients had higher mean rise time, a slightly higher mean age, and a lower mean 6-minute walking distance compared to study 1 and 2. I will be discussing each study in this presentation.

The application also included an open label extension of study 1 and 3 that continued for a little over 2 years. The study was terminated after the negative results of the large phase 3 study; hence, not all subjects completed 96 weeks of the study. Forty-three percent dropped out by week 96, and 76 percent dropped out by week 120 of the study.

I will now briefly discuss the results of each study. Let us look at the results of the clinical endpoints.

Study 1 evaluated two regimens of the same dose, 6 milligram per kilogram, referred to as the continuous and intermittent regimen. Each treatment arm had about 17 to 18 patients. I remind you again that a loading dose was administered to all patients in this study.

On this slide, drisapersen continuous regimen is shown in red, drisapersen intermittent regimen is shown in green, and placebo is shown in blue. The primary endpoint, change from baseline 6-minute walking distance, was positive at week 24 for the 6 milligram per kilogram per week continuous regimen, with a p-value of 0.01 and a treatment difference between drisapersen and placebo of 35 meters. You can see an increase in 6-minute walking distance was observed in the continuous regimen starting week 13.

The primary endpoint was negative for the intermittent regimen, with a p-value of .8 and a treatment difference of 4 meter, as shown in the green curve. The p-value at week 24 must be interpreted in the context of multiple comparisons.

Since there were two regimens of the same dose, the comparison of each dosing regimen and placebo was adjusted using Bonferroni-Holm adjustment for multiplicity. The statistical significance level was therefore set to 0.025.

Overall, we find the persuasiveness of study 1 to be low for the reasons I will describe in the following slides.

For study 1, a concern was that the continuous arm comprised of more patients with higher function at baseline. In Duchenne muscular dystrophy, it is known that patients that are more functional at baseline have slower progression and better prognosis.

The table in this slide shows the percentage of patients with some key prognostic factors that could suggest better prognosis. As we can see in the column in the grey-shaded area, which shows the continuous arm, there were greater number of patients in that arm that were less than 7 years.

Patients less than 7 years tend to improve in function due to growth and maturation effects;

therefore, also greater number of patients who had a baseline 6-minute walking distance of greater than 400 meters and a baseline rise time of less than 4 seconds in the drisapersen continuous arm. Also, more patients of that arm were on continuous steroids. Patient on continuous steroids do better than those on intermittent steroid regimens.

We also looked at other factors that also suggest that the patients in the continuous arm could be more functional at baseline. These include the ability to jump with both feet up at the same time, the ability to hop with clearing foot and heel from the floor, and the ability to rise from the floor without Gower's maneuver. A much larger percentage of patients in the continuous arm could perform these tasks.

In addition, I would like to point out that the patients on the intermittent regimen had a smaller percentage of patients that could perform the tasks shown in green than the patients in the placebo arm. We believe that these differences may have an impact on the disease trajectory of these

patients regardless of the treatment they receive, and favored the continuous drisapersen arm.

Another factor that decreases the persuasiveness of the findings is the low internal consistency of the study. The first reason, which is critical in my opinion, is that the intermittent regimen, that had the same total number of doses as the continuous regimen and produced the same plasma concentration as the continuous regimen, was no better than placebo in study 1.

At the late cycle meeting, the applicant indicated that the muscle drug distribution of the intermittent regimen could be different. However, the muscle drisapersen concentration at week 24 for the intermittent regimen was similar to the continuous regimen. Hence, the lack of effect of the intermittent regimen questions the effect seen in the continuous group.

In addition, the secondary endpoints were all statistically nonsignificant. As we can see, the North Star Ambulatory Assessment total score and all time function tests were statistically

negative for both the continuous and the intermittent arm.

As we can also see, the treatment difference between drisapersen and placebo were very small and mostly less than 1 second for the time function test. For the endpoints shown in red, placebo was numerically better than drisapersen.

The applicant conducted a 48-week post hoc analysis. There was a treatment difference of 36 meters for the continuous regimen and a 27-meter treatment difference for the intermittent regimen. However, this post hoc analysis is statistically uninterpretable.

The subjects of study 1 were also evaluated in an open label extension, where all patients had the option to switch to drisapersen 6 milligram per kilogram per week continuous treatment, which is illustrated in this slide.

The back dashed vertical line is the point when all patients from the double-blind study were switched to active treatment in the open label extension study. The extension study does not

provide interpretable evidence of efficacy.

As argued by the applicant, a 50-meter treatment difference was observed for the continuous treatment arm, shown in red, compared to the placebo arm, shown in blue, at week 48 of the extension study. However, we cannot ignore the trajectory of the intermittent arm, as shown in green, and the placebo arm, as shown in blue, during the active treatment extension phase.

Patients randomized to placebo or intermittent drisapersen were fairly stable during the double-blind phase of study 1 but appeared to decline more rapidly when on continuous drisapersen treatment in the extension phase, which argues against efficacy of continuous drisapersen.

By the end of the extension phase, patients who were originally randomized to intermittent drisapersen are numerically worse than patients who were originally randomized to placebo. In addition, the trend towards benefit observed with the intermittent regimen at week 48 of the double-blind phase looks like background noise, as that

group rapidly declined in the extension phase while on continuous drisapersen.

Even if we were to ignore the first part of the study and consider that these placebo subjects were recruited afresh and administered drisapersen 6 milligram per kilogram per week, one would not expect these subjects to decline by 30 meters in one year if we believed the results of the red curve.

In general, our main concern is that it is difficult to interpret efficacy in an open label extension. Since the extension study was terminated, two or three subjects were lost in each arm in the extension phase by week 48, which add to the complexity in interpreting the study.

Now let us look at the second study. This study evaluated a 3 and 6 milligram per kilogram per week dose of drisapersen versus placebo, with a 24-week treatment period and an additional 24-week observation period. Subjects were not given a loading dose in this study.

In study 2, the p-value for the primary

endpoint change from baseline 6-minute walking distance at 24 weeks was negative for both driven groups. There was a trend favoring drisapersen 6 milligram per kilogram, with a p-value of 0.07, but a number of findings in study 2 argue against efficacy of drisapersen.

First, one patient assigned to the placebo group was unblinded after a hospital visit, and therefore was removed from the per-protocol analysis. With that single patient removed, the treatment effect of the 6 milligram per kilogram drisapersen group goes down to 19 meters, with a p-value as high as 0.23.

Even more concerning, the 6 milligram per kilogram per week was numerically inferior to placebo on most secondary endpoints. Also distressing was the fact that the 3 milligram per kilogram group was numerically inferior to placebo.

This slide illustrates the secondary endpoints in study 2. For the endpoints shown in red, drisapersen was numerically worse than placebo. The drisapersen arm was numerically

better than placebo for the four-stair climb, ascent and descent, but the treatment effect was small, less than 1 second, and the differences were not statistically significant.

Now let us look at the results of the large phase 3 study. It is highly concerning that this large study, which was well powered and balanced for prognostic factors, was negative at week 48, with a p-value of 0.42 and a 6-minute walk test difference between drisapersen and placebo of just 10 meters.

There was no trend favoring drisapersen for any of the secondary endpoints in study 3. Half the secondary endpoints went in the wrong direction, with placebo numerically better than drisapersen, as shown in red.

The applicant provides various explanations for the negative results of study 3. First, the applicant argues that the results were impacted by the fact that patients in study 3 had, on average, more advanced DMD. As we discussed earlier, study 3 had no restrictions on the rise from floor

time at enrollment, and patients therefore had greater functional impairment at baseline. The applicant suggests positive results if a subset of more functionally impaired patients is eliminated.

The second explanation is that the treatment duration of 48 weeks was not sufficient to show a treatment effect in a more heterogeneous population. The applicant's rationale includes the open label extension study of study 3 that showed a 30-meter difference between the treatment groups at week 96 of the study.

The third proposed explanation is that there was varying expertise in centers who participated in study 3. The applicant proposes that a post hoc analysis limited to phase 2 study site gives a close to nominally p-value.

The last explanation from the applicant is the lack of a loading dose in study 3. Other than study 1, none of the studies had a loading dose.

In the subsequent slides, I will discuss our thoughts on each of these arguments.

The applicant's first explanation was the

inclusion of a population with greater functional impairment at baseline. Due to the lack of restriction of the rise from floor time at enrollment, the phase 3 study indeed included patients that were more impaired at baseline.

Therefore, to assess the applicant's argument, we conducted an analysis of study 3, removing patients that were most impaired. In order to do that, we kept only patients that matched the phase 2 population. This translates into a baseline age range of 5 to 13 years, a 6-minute walking distance range of 300 to 561 meters, and a rise from floor time of up to 7 seconds. This made the type of patients enrolled in the phase 2 and 3 studies similar with regard to the key prognostic factors.

Our analysis is shown on this slide. It includes about half of the patients who participated in study 3. This analysis shows a treatment difference of 5 meter and does not support efficacy of drisapersen in these less severely affected patients.

To explain the enrollment of the more advanced DMD patients, the applicant also argues that a larger treatment difference was observed in patients less than 7 years of age, which are likely to be less impaired. As we can see on this slide, there was no consistent evidence that a larger effect was observed in subjects less than 7 years.

In study 1, a larger effect was observed in subjects greater than 7 years, with the caveat that the sample size was small, and in study 2, no appreciable difference was observed between age groups.

In addition, polling study 1 and 2, a larger difference was observed in subjects greater than 7 years. Therefore, the use of age as a post hoc cutoff is not justified because there is no consistent effect of age in other studies.

The applicant conducted many post hoc analyses to address the concern of the enrollment of patients with more advanced DMD. The statistician, Dr. Yan, will now talk about the applicant's post hoc analyses on the study.

FDA Presentation - Sharon Yan

DR. YAN: Good morning. My name is Sharon Yan, and I'm the statistical reviewer of this submission.

The sponsor has made some arguments about efficacy of the phase 3 trial using some post hoc analysis to explain some negative findings of the phase 3 trial. I will not discuss whether these post hoc analyses are reasonable. I will just present to you a couple of examples and to ask you to think about whether these arguments could hold and whether the results from those analyses are interpretable.

One of the arguments the sponsor made is that drisapersen seems to work except for the older and more impaired patients. By looking at this particular grouping of subgroups using the age and the baseline in combination, it shows there is positive treatment difference in all groups except group 3, with older and more impaired patients. By excluding the patients in group 3, the nominal significance is reached.

Unlike prespecified and well-planned subgroup analysis normally used to examine the consistency of the treatment effect, such post hoc subgroup analysis could be sensitive to the cutoff point chosen and rely heavily on the balance of the group.

In this particular grouping, the number of outpatients in group 1 is less than half of the patients in any other groups. Within group 1, placebo patients constitute less than 20 percent of the total. Among the four placebo-treated patients, one broke his leg during the trial and couldn't perform the assessment afterwards, resulted in a large negative change of 184 meters.

Further, there seemed to be contradictory results, as among the younger age patients of age 7 and under, drisapersen appears to work better among the more impaired patients, as we can see the results of group 1 versus group 2. And in the older age patients, drisapersen appears to work better in less impaired patients, as the result shown in group 3 versus group 4.

We further examined the arguments by selecting the different cutoffs, slightly lower and slightly higher. In both cases it led to a large swing of treatment difference. Here is shown the results from slightly high cutoffs of baseline walking distance at 350 meters, and we see the large difference of treatment effect in group 1 and group 4.

Most importantly, the rationale of excluding patients in group 3 no longer holds as group 3 is not the only group that lacks the efficacy. Negative results are shown in both group 3 and group 4. Combined, they constitute the majority of patients.

There are various other subgroup analyses that can be performed by using different cutoff of the baseline walking distance, as shown in one of the analysis the sponsor presented to us, looking at a subgroup of patients with baseline walking distance between 300 meters and 400 meters. This analysis yielded a much larger treatment difference of 28 meters compared to 10 meters from the primary

analysis.

However, if we look at the subgroup outside of this range, for patients less than 300 meters or more than 400 meters, or we look at patients whose baseline walking distance is 330 meters or above, or we simply just change the lower bound of the sponsor's range from 300 meter to 330 meters, all these analyses yielded much smaller treatment difference, smaller than the one from the primary analysis.

Another argument the sponsor made is that more patients in the drisapersen group compared to placebo group had increase in walking distance at week 48, 37 percent in the drisapersen group versus 24 percent in the placebo group who had at least 1 meter of increase in walking distance, a difference of 13 percent.

We looked into those patients to see how much improvement they made. It occurred that among the patients who had increase in walking distance, placebo-treated patients had a larger increase than the drisapersen-treated patients in both mean and

the median for at least 13 percent.

As we can see now, there are unlimited number of post hoc analysis we can perform. None of them can answer our question whether the drug works. And then none of them provided convincing evidence.

Should we perform any post hoc analysis at all? There are two possible reasons to conduct post hoc analysis of a failed study. One is to find an analysis with a better or more significant p-value to support approval.

As there are unlimited number of analyses that can show one group is better than the other, perhaps as many analyses to show just the opposite, that the p-values are meaningless, as type 1 error could be near 1. And most of these analysis do not address any meaningful question.

Another possible reason is to identify a subgroup of patients for which the drug appears to work. The focus of such analysis should not be to decrease the p-value. Effort should be made to identify possible causes of study failure.

If we can identify the possible causes of failure and to identify the subgroup the drug might work, we will give us a much better odds for the next study to be successful and to be able to replicate the positive findings if the drug truly works.

Thank you. Dr. Tandon will continue the remaining of the clinical efficacy discussion.

FDA Presentation - Veneeta Tandon

DR. TANDON: As I had mentioned earlier, the applicant had proposed a number of possible explanations for the negative results of study 3. One of those is the inadequacy of the treatment duration of study 3.

The open label extension of study 3 conducted by the applicant is proposed as supporting evidence of efficacy with the longer treatment duration, with a mean difference between drisapersen and placebo of 30 meters on the 6-minute walking distance test.

I would like to point out that though the main treatment difference was 30 meters, the median

treatment difference at week 48 of the extension study was only 9 meters. Also, the interpretation of the open label studies for efficacy is problematic, as explained earlier with regards to study 1 extension phase.

An additional concern comes from the higher dropout rate of 43 percent at week 96 and 76 percent at week 120. This makes the trial results impossible to interpret.

In addition, the apparent treatment difference appeared early in the phase 2 studies, and there is no convincing reason to believe that efficacy would be delayed beyond 48 weeks of treatment. Moreover, study 3 was adequately powered to detect a treatment difference.

The applicant's third argument is that the involvement of multiple centers with varying degrees of expertise in treating DMD may have affected the results. The applicant suggests that there is stronger evidence of efficacy from the study sites that also participated in phase 2 studies.

The applicant's post hoc analysis on a very small fraction of patients, just 16 patients on drisapersen and 9 patients on placebo out of a total of 186 patients, is completely uninterpretable. In addition, there is no evidence of efficacy in data quality amongst clinical sites who participated in the studies.

The applicant's last explanation was the lack of a loading dose. We do not believe this argument has value. The intermittent regimen group, which received a loading dose, had no treatment benefit. The study 2 also had no loading dose.

The plasma and muscle concentrations from drisapersen 6 milligram per kilogram in each study was similar with or without loading dose, which further weakens the argument that the lack of loading dose played any role in the study results. The application also included a historical control, 3-and-a-half-year long study in 12 subjects, which is ongoing.

Before I discuss the results of the

historical control study, let me point out the limitations of historical control studies, which are well-recognized and discussed in the ICH E10 on the choice of control group and related issues in clinical trials.

That guidance describes that the inability of such studies to control bias is the major and well-recognized limitation, and is sufficient in many cases to make the study unsuitable. The guidance explains that it's always difficult and in many cases impossible to establish comparability of treatment and control groups.

The guidance goes further to say that it is well documented that the untreated historical control groups tend to have worse outcomes than an apparently similar chosen control group in a randomized study, and that an external control group is often identified retrospectively, leading to potential bias in selection.

Finally, the guidance stresses a very important point, that the inability to control bias restricts the use of external control design to

situations in which the effect of treatment is dramatic and the usual course of the disease is highly predictable.

Keeping these limitations in mind, let us look at the results of the historical control study. The study 3 was 3 and a half years long and included 12 subjects. The applicant argues a divergence between patients on drisapersen and natural history. The applicant classified patients as stable and declining at the start of the study based on clinical judgment.

As seen in the table below the figure, seven subjects were classified as stable and five as declining. Two patients lost ambulation in early part of the study. The stable group showed a median improvement of 91 meters and a mean improvement of 45 meters, whereas the declining group had a median decline of 243 meters and a mean decline of 187 meters.

As we can see in the table, the declining patients were older, with the mean age of 11.8 years, and more impaired, with the a lower 6-

minute walking distance of 217 meters, and higher rise from floor time than the stable patients, who had a mean age of 8.8 years.

The subjects in the stable group had an unusually low mean rise from floor time of 2.4 seconds. We know that the low rise time is an indicator of muscle strength, and it is now well understood that the stability of the patients over time is greatly influenced by baseline factors.

Dr. McDonald and others have presented and published on the natural history of DMD extensively. A quote from published article is that, "The higher baseline function is almost always associated with slower long-term decline in DMD."

The 6-minute walking distance of each subject for 3 and a half years is shown in the figure on this slide. The results in the historical control study appear biased and are in fact expected, regardless of treatment, due to the baseline characteristics of the well-preserved stable patients enrolled in the study.

This slide shows the comparison of the stable patients in the historical control study to the placebo patients from study 3 who were of similar age, greater than 7 years, with 6-minute walking distance between 300 and 500 meters, and rise from floor time of less than 5 seconds.

The left panel shows the 6-minute walking distance for 48 weeks from the placebo patients from study 3 that could be identified with low rise times. The right panel shows the 6-minute walking distance from stable patients in the historical control study. The rise time from the placebo patients were 3.1 to 4.7 seconds, and the rise time from the stable patients were 1.7 to 2.9 seconds.

Even though the placebo patients that could be identified had slightly higher rise time than patients on drisapersen, the disease trajectories appear similar. Improvement in 6-minute walking distance of up to 100 meter in one year is seen in placebo patients with low rise times.

We also combined all the placebo data from the drisapersen studies and categorized the placebo

patients in various bins according to the baseline rise time and plotted 6-minute walking distance as a function of age. We then superimposed the historical control patients according to their rise time, 6-minute walking distance, and age.

This slide shows the patients with rise time of less than 3.6 seconds. The placebo patients are shown in grey lines, and the patients on drisapersen from the historical control study are shown with colored lines.

As we can see, the patients on drisapersen in the historical control study have generally similar course to patients on placebo to the degree that patients could be matched to baseline rise time, 6-minute walking distance, and age.

Please note that the patients in the historical control study had lower rise time than the placebo patients, which suggests a slower decline expected in these patients. The maximum rise time in the historical control study in the stable patients was 2.9 seconds. We could only find three placebo patients with a rise time lower

than 2.9 seconds.

This slide shows the trajectories of 6-minute walking distance in patients who were on placebo and had a rise time between 3.7 and 7 seconds at baseline. There is a notable lack of patients in the midrange of rise time, between 3.7 and 7 seconds, in the historical control study.

This slide shows patients with rise time greater than 7 seconds. Patients on drisapersen in the historical control study also have a disease course generally similar to patients who are on placebo in study 3.

Next, I will discuss the biomarker data. Before I discuss the dystrophin results, Dr. Rao from the Office of Biotechnology Review and Research will discuss the dystrophin methodologies involved in the assessment of dystrophin.

FDA Presentation - Ashutosh Rao

DR. RAO: Thank you. Good morning. My name is Ashutosh Rao. I am a researcher and reviewer in the Office of Biotechnology Products here at FDA. I provided the clinical review team with a consult

review of the dystrophin bioassays and supporting assay validation data.

Before we discuss the dystrophin data from each of the applicant's clinical studies, my task here is to set the stage and provide you with a high level overview of our understanding of the applicant's methodological approaches and our current thinking of the extent to which they are capable of reliably indicating whether and how much exon skip dystrophin was produced, which is the applicant's proposed mechanism of action. Dr. Tandon will follow up with individual drisapersen study data.

Dystrophin and its measurement is a complex and evolving topic. This is a quick overview of our current understanding of what is known in the literature about ways to measure dystrophin and the applicant's dystrophin methodologies.

I will not go into the biochemistry involved here, but based on literature and input from scientific experts, a scientifically credible review of dystrophin levels requires that the

method or methods be capable of answering these basic questions.

What were the relative levels of dystrophin mRNA protein before and after treatment? How do the levels of protein compare to a healthy level of dystrophin? Is the newly expressed dystrophin distinct and above any trace or revertant dystrophin? Was the newly expressed dystrophin localized to the cell membrane?

The applicant tested for relative dystrophin expression by measuring mRNA protein levels using polymerase chain reaction, PCR, immunofluorescence, and western blotting. They also tested for the localization of dystrophin to spectrin and of the cell membranes by immunofluorescence. The revertant fibers, which contain dystrophin from rare, spontaneous restoration of dystrophin in DMD patients, was also measured with immunofluorescence.

I have three slides coming up that summarize our current view of the applicant's dystrophin methods and the supporting assay validation data

presented to us. Before I speak to the methods, here are some caveats that it would be reasonable to point out that are challenges in general for current dystrophin methodologies and should be considered while the totality of the applicant's dystrophin evidence is weighed.

Currently, individual dystrophin methods are somewhat limited in their accuracy because no reference standard is available for accurate comparison. We don't know whether the new protein seen in cells is actually functional.

It's unclear whether the new dystrophin is from revertant fibers or drug-induced. Quantitation at very low levels can be challenging. Both dystrophin and sample heterogeneity are challenges. And other biological factors, such as the pro-inflammatory environment of the muscle fiber and contributions of other proteins towards dystrophin expression, remains to be properly defined.

While individual methods have their challenges, it is our current understanding that

the use of multiple dystrophin bioassays may allow a reasonable estimate of its location and amount.

On each slide, I will show a typical data image that was reviewed, along with a summary of our current thinking of whether their approach was analytically capable of providing meaningful results.

Here is a snapshot of the applicant's RT-PCR approach for measuring whether and to what extent the drug generated an exon 51 skipped transcript. The applicant provided data with two methods, a nested RT-PCR and an exploratory Droplet Digital PCR.

The nested PCR was designed to provide a qualitative confirmation of the skip product. The applicant did go ahead and quantify the skip band, which would be the lower band in, say, lanes 2 and 3 shown on the image there, to get an estimate of the extent of skipping.

The proposed acceptance criteria for considering a positive skip was if the band intensity was greater than 1 percent over a

baseline sample, which suggests a very sensitive assay. Only a small subset of samples was also tested with a Droplet Digital PCR, which was presented to us by the applicant as an exploratory method.

Based on the method development and assay validation information provided, we currently believe that the applicant's nested PCR method is capable of providing a qualitative confirmation for the presence of skipped dystrophin band. It should be noted that the method does not indicate the stability of this very large transcript or whether the mRNA was actually translated into a functional protein.

The applicant tested for dystrophin protein levels using immunofluorescence, where mean intensity of the membrane-associated dystrophin was used as a readout. Spectrin co-localization was used as a marker of membrane localization. The revertant fibers were reported as percent revertance and as part of the total membrane intensity.

Based on their validation, their assay variability was between 3 and 11 percent. Using this information, the acceptance criteria for a positive score was greater than 4 percent increase in intensity over baseline. So the assay is proposed to be sensitive to very small changes.

Overall, we consider that the applicant's immunofluorescence method is capable of reliably indicating the membrane-associated localization of dystrophin, and that if increases are observed over their predetermined assay variability, they are likely to reflect analytically true responses.

It should be clarified here that the 4 percent increase over baseline is not the same as a 4 percent increase over a healthy or relative to a healthy or normal sample. To put that in perspective, a 4 percent change from baseline would theoretically translate to a change from a 1 percent in pre-treatment to a 1.04 percent in a post-treatment relative to normal, which would be a very small change.

The applicant also tested for total

dystrophin levels by western blotting using a sensitive LICOR-based assay. A serially diluted healthy muscle lysate was included on each gel, which is towards the left-hand side of the image that's shown. This was done for comparison and for relative quantitation, their predetermined assay variability being 25 percent. Their acceptance criteria for a positive response was greater than 30 percent over baseline.

They also reported that their lower limit of detection was 1 percent of healthy, which seemed reasonable. To put that in perspective again, if a pre-treatment sample was 1 percent of healthy and a post-treatment sample was 1.3 percent of healthy, it would be considered to meet the applicant's acceptance criteria for a positive score.

In BioMarin's current application, the combination of western blot and immunofluorescence methods is reasonably well suited to provide the location and an estimate of total dystrophin levels before and after treatment. The western blotting is more likely to be quantitative because of the

inclusion of a serial dilution of healthy control lysates.

The acceptance criteria or cutoffs for a positive scoring appears to be analytically reasonably determined based on the supporting assay validation data provided.

Dr. Tandon will now present the dystrophin results from the individual drisapersen studies.

FDA Presentation - Veneeta Tandon

DR. TANDON: The dystrophin data from all the studies were very inconsistent. As Dr. Rao just mentioned, the detection of dystrophin was assessed by exon 51 skipping by mRNA, qualitative immunofluorescence, and by western blot.

A score of positive response was based on the acceptance criteria, as determined by the applicant. As Dr. Rao mentioned, each method had a different cutoff for an increase in intensity from baseline, as determined by the assay validation.

By PCR, there was no consistent trend between treatment groups. In study 1, only 2 out of 18 subjects showed an exon skipping on

drisapersen and none on placebo. In study 2, 10 subjects showed exon skipping on drisapersen and two on placebo. As we can see for study 3, 56 out of 61 placebo subjects showed exon 51 skipping, while 114 out of 125 on drisapersen showed exon skipping. This study did not have any pre-treatment values.

All subjects had a biopsy at the end of study at week 48, and an additional biopsy at either week 8, 12, or 36. Looking at subjects that had a week 8 biopsy, no consistent trend of increase in intensity from week 8 to week 48 was observed in drisapersen-treated patients.

With the lack of pre-treatment biopsy in all subjects with PCR, it is difficult to determine the true exon 51 skipping due to drisapersen was a spontaneous exon skipping activity due to trace dystrophin.

For immunofluorescence in study 1, 9 out of 15 patients showed an increase in intensity on drisapersen versus 1 out of 18 in the placebo group. In study 2 and 3, however, more subjects on

the placebo group showed an increase in intensity than patients on drisapersen, as shown in the red circle. Note that IFA can suggest protein localization, but is less meaningful for protein quantification.

By western blot, only study 1 showed an increase from baseline, and this was noted in only 5 out of 17 patients on drisapersen continuous treatment. In the subsequent slide, I will talk more on the western blot data.

In study 2, 66 percent of the patients had an acceptable biopsy for the analysis of dystrophin expression, but none on western blot showed a positive response with drisapersen 6 milligram per kilogram.

Even though a small increase in dystrophin from baseline was seen by western blot in 5 out of 17 treated patients in study 1, the increase appeared to be extremely small compared to levels seen in healthy controls, as shown on the figure on the slide.

All drisapersen pre-treatment levels were

less than 1 percent, and almost all post-treatment levels were also less then 1 percent of normal. There were 5 subjects on the intermittent regimen that also showed pre- and post-treatment levels of less than 1 percent of normal, but we know that the patients on the intermittent regimen did not do well either in the one-year study or in the two-year extension phase of the study.

It is also known that trace levels of dystrophin, typically around less than 1 percent of normal, are present in many DMD patients. A few patients in the drisapersen studies had higher baseline dystrophin, between 1 and 4 percent, but these patients did not show any detectable post-treatment change.

Next, moving to the serum markers of muscle injury such as serum creatinine kinase and lactate dehydrogenase.

Serum creatinine kinase is used as a diagnostic marker in DMD. Dystrophin deficiency and associated muscle fiber damage in DMD results in the release of muscle-specific enzymes such as

CK out from the muscle fibers into the circulation, causing an increase in CK in DMD patients by 10- to 100-fold of normal. It is hypothesized that an improvement in membrane integrity induced by production of dystrophin could result in the reduction of serum CK.

There was a consistent 30 to 40 percent decrease in CK across all three placebo-controlled studies. We do not know what caused the changes in CK level in the drisapersen studies. CK is known to change due to a variety of factors, example: muscle injury, physical activity, age, and loss of muscle mass. There is no relationship between a person's CK reduction and the change in 6-minute walking distance in drisapersen studies.

The Y-axis in the figure on this slide shows the percent reduction in CK in individual patients on drisapersen, shown in the left graph with red symbols, and on placebo, as shown in the right graph with blue symbols. The change from baseline 6-minute walking distance is plotted on the X-axis. As we can see, more patients on drisapersen had a

reduction in CK compared to placebo.

But it is noteworthy that similar magnitude of decline in CK of about 70 to 80 percent was observed in many individual patients, both in the drisapersen group and the placebo group. And the change from baseline 6-minute walking distance was much worse in many subjects that showed greater decline in CK, as seen in the left bottom portion of the graph.

If a relationship were to be found, then most patients should be present in the right bottom quadrant of the figure. Therefore, there is no relationship between the reduction in CK observed in drisapersen studies and the change in 6-minute walking distance. The clinical significance of the reduction in CK is not understood, but does not appear to be related to any treatment benefit.

Thank you. Now Dr. Mentari will present the safety review for drisapersen.

FDA Presentation - Evelyn Mentari

DR. MENTARI: Good morning. My name is Evelyn Mentari, and today I will discuss the

clinical safety of drisapersen. The main safety concerns that I will discuss today include thrombocytopenia, renal toxicity, injection site reactions, and vascular inflammation.

First, I will discuss thrombocytopenia. Please note that the unit of measure for each platelet count that I will discuss is 10 to the 9th cells per liter.

In placebo-controlled studies, thrombocytopenia was reported in 10 percent of drisapersen patients compared to 3 percent of placebo patients. Patients received drisapersen for up to 11 months in placebo-controlled studies.

In this time period, no patient had platelet counts less than 75, the level below which primary hemostasis is generally considered to be impaired. However, in uncontrolled extension studies, 6 patients had platelet counts less than 20. These cases occurred after 14 to 26 months of drisapersen treatment.

Bleeding in these patients included epistaxis, hematemesis, petechiae, and gingival

bleeding. Platelet counts less than 20 put patients at risk for potentially fatal complications, including spontaneous intracranial or intrapulmonary hemorrhage. Of the 5 patients tested for antiplatelet antibodies, 4 had a positive result.

The time course of thrombocytopenia with drisapersen can be unpredictable, and the decrease in platelet count can be precipitous. Patients can have consistently normal platelet counts, including a normal platelet count within 2 weeks of developing thrombocytopenia.

This slide displays platelet counts in an individual patient who developed severe thrombocytopenia. The Y-axis shows the platelet count, the X-axis shows the study day, and the grey horizontal lines indicate the range of normal laboratory values for platelet.

At 16 months of treatment, this patient had a normal platelet count of 161. Two weeks later, his platelet count was 56 and drisapersen was discontinued. His nadir platelet count was 5,

which occurred 16 days after stopping treatment. He received antifibrinolytic therapy with tranexamic acid, and improvement to a level greater than 20 occurred 4 weeks after stopping treatment.

This slide shows the time course of severe thrombocytopenia in a second patient. After 13.5 months of drisapersen treatment, he had a normal platelet count of 198. Two weeks later he had a platelet count of 18, and drisapersen was discontinued. The nadir platelet count was 14, which occurred 4 weeks after stopping treatment. Improvement to a level greater than 20 occurred 6 weeks after stopping treatment.

Platelet counts were routinely measured every 2 weeks in the drisapersen development program. Platelet counts every 2 weeks could mitigate the risk of bleeding but not eliminate it.

Next, I will discuss renal toxicity. The kidney is a target organ of drisapersen, which accumulates in the proximal tubule. Thirty percent of patients who received drisapersen had an abnormal 24-hour urine protein compared to

4 percent of placebo patients. Clinical studies had treatment stopping criteria based on quantitative urine testing, scheduled every 2 weeks.

Two patients had serious nephrotic range proteinuria related to drisapersen. In the published literature, thrombotic events complicate the nephrotic syndrome in approximately 25 percent of patients.

Patient 1 was diagnosed with membranous glomerulonephritis with a urine protein, up to 9 grams per day, after 29 weeks of treatment. His proteinuria and clinical condition worsened for one month after drisapersen treatment was discontinued. At that time, he developed potentially fatal bilateral pulmonary emboli and thromboses of the inferior vena cava and right renal vein. His proteinuria resolved 8 months after drisapersen discontinuation.

Patient 2 had severe proteinuria, up to 11 grams per day, after 54 weeks of treatment. No kidney biopsy was performed, so the underlying

pathologic diagnosis was not evaluated in this patient. His proteinuria resolved 3 months after drisapersen discontinuation.

While the proteinuria resolved in these patients, it is unclear whether underlying pathologic abnormalities persist, which may increase the risk of future kidney disease in these patients.

To monitor for renal toxicity, renal testing at baseline and every 2 weeks would be necessary because of the potential for rapid progression of renal toxicity; a time period of worsening renal toxicity after a drisapersen treatment discontinuation; and serious, potentially fatal consequences of renal toxicity.

Next, I will discuss injection site reactions, which occurred in 79 percent of drisapersen patients. The most common injection site reactions reported were erythema, discoloration, pain, and pruritis. Chronic skin damage, including atrophy, decreased fat tissue, injection site nodules, hypertrophy, plaques,

calcifications, scars, masses, acquired lipodystrophy, and skin fibrosis occurred in 18 percent of drisapersen patients. Ulceration occurred in 7 percent of drisapersen patients.

The next few slides show injection site reactions in drisapersen patients. This slide shows injection site ulceration of the leg, this slide shows injection site discoloration, and this slide shows another case of injection site ulceration.

Two patients had injection site reactions requiring hospitalization. Patient 1 had severe arm edema with fever, and patient 2 had severe arm edema with infiltration of subcutaneous tissues by ultrasound. Twenty-one percent of injection site reactions were not resolved at the end of studies. Injection site reactions known to resolve lasted for a mean of 2 months and up to 3.3 years.

Injection site reactions occurred despite administration of drisapersen by medical professionals. Rotation of injection sites is necessary, but can lead to toxicity to large areas

of skin. No other strategies have been identified to mitigate injection site reactions.

Next, I will discuss vascular inflammation. In nonclinical studies, inflammatory effects of drisapersen were evident in mice and monkeys in numerous tissues, including kidney, liver, injection site, and the vasculature. Vasculitis was evident in multiple organs in the monkey. Coronary arteritis resulted in thrombus formation, myocardial necrosis, and in some animals, premature sacrifice.

In clinical studies, serious adverse reactions in drisapersen patients with vascular inflammation as a possible etiology included myocardial ischemia, intracranial venous sinus thrombosis, small intestinal obstruction, and myocarditis.

In conclusion, severe and potentially life-threatening adverse reactions occur with drisapersen, including thrombocytopenia, renal toxicity, injection site reactions, and several serious adverse reactions with vascular

inflammation as a possible etiology. Periodic monitoring of platelet count and urinary protein would be essential, and monitoring could mitigate but not eliminate these risks. Thank you.

Clarifying Questions

DR. ALEXANDER: Thank you. I'd like to thank the FDA for their presentation.

Are there clarifying questions for the FDA? Again, please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

Dr. Hoffmann?

DR. HOFFMANN: I had two questions to a specific presenter. This is Richard Hoffmann. Two questions for Dr. Tandon.

My first question is, I'm a little confused about the dystrophin expression in study 1. Patients who received the drug had a 7 percent difference compared to placebo in dystrophin expression by immunofluorescence. Are you saying that that's not clinically important or meaningful?

Number two, in study 1 also, in the

intermittent regimen, patients were off the drug for a 4-week period out of 10 weeks. Do you think that this would have changed the pharmacokinetics of the drug, which might have led to the negative results in the intermittent regimen? Thank you.

DR. TANDON: Slide 41 of the main deck, please. Yes. So your question was 7 percent? I didn't get your question on the dystrophin.

DR. HOFFMANN: Yes. The 7 percent difference between placebo -- the question, was the amount of dystrophin production in study 1 across the arms?

DR. TANDON: It's not a difference in percentage here. It shows the number of subjects that showed a positive increase based on the analytical validation.

DR. HOFFMANN: I thought it was a percentage --

DR. ALEXANDER: Can you use the microphone, please?

DR. HOFFMANN: I thought it was a percentage increase.

DR. TANDON: Percentage increase, but these are the number of subjects. If you look at the table at the top, it says number of subjects, or the total number of subjects that actually showed a response, an increase in intensity from baseline, based on the analytical validation.

So it was 7 subjects out of 12 in the placebo group that actually had an increase in intensity from baseline, and there was only one subject out of 18.

DR. HOFFMANN: I thought it was a 3.9 percent increase in dystrophin expression compared to a negative 3.1 percent in the expression for placebo, which would be a 7 percent --

DR. TANDON: No. I think this is number of subjects. The slide shows the number of subjects. I'm not talking in terms of percent increase.

DR. HOFFMANN: But in the applicant's briefing documents, that's what they specify.

DR. TANDON: So the applicant is -- in their briefing document, they show the percentage

increase from baseline. It is not compared to normal. So as you recall Dr. Rao's analytical validation slides, he talks about what the analytical limit was. For immunofluorescence it was increase in intensity over 4 percent.

DR. HOFFMANN: So you're saying that's not clinically meaningful?

DR. TANDON: It is increase from baseline. It is not compared to normal.

DR. ALEXANDER: Thank you. And then there was a second part to the question, which was regarding in study number 1, there were 4 weeks off of drug of the 10 weeks in the intermittent regimen. And the question was whether that could have changed the pharmacokinetics in a way that accounted for the findings.

DR. TANDON: No. Actually, it didn't. The plasma concentration time profile for the continuous and intermittent regimen was identical. So that really didn't change the plasma concentration profile. I don't have the profile with me here.

DR. HOFFMANN: Yes. To me, it seems -- I know both groups got the same drug exposure. But when you're off the drug --

DR. TANDON: The drug has a long half-life, so probably that takes care of the dosing interruption and doesn't affect the plasma concentration profile as much.

DR. HOFFMANN: Thank you.

DR. ALEXANDER: Thank you for the question.

Dr. Ovbiagele?

DR. OVBIAGELE: Thank you. Dr. Tandon, if you adjust for the differences in the imbalance in terms of the predictors of good function at baseline between the continuous and the placebo, does the beneficial effect in study 1 go away?

DR. TANDON: The sample size is too small to really adjust -- put those into the model. But although the statistician can talk about it, I think they did include 6-minute walking distance in the model. But the baseline imbalances I talk about looks at many factors that suggest that the patients were more healthy.

DR. YAN: My name is Sharon Yan. I'm the statistical reviewer. In study 1, it appears that for the baseline, the drug group has some benefit versus the placebo group in terms of baseline walking distance.

DR. TEMPLE: So you don't mean benefit. You mean advantage. Right? You mean at baseline, they were slightly better. Right?

DR. YAN: It is better for the drug group in terms of baseline walking distance and the age.

DR. ALEXANDER: And the question was about whether, if one adjusts for those differences, differences between the groups at baseline, does the efficacy difference diminish or disappear?

DR. YAN: For the study 1?

DR. ALEXANDER: Correct.

DR. YAN: For the study 1, it seems to be that even though adjusted, the results don't change much.

DR. ALEXANDER: Thank you.

Dr. Kesselheim?

DR. KESSELHEIM: Thank you. Aaron

Kesselheim. My question was also on slide 41. I was wondering if you could comment on the consistency in when the biopsies were done and the technique and procedure for doing the biopsy.

DR. TANDON: I think the sponsor will be better to answer that question, or Dr. Rao.

DR. RAO: I think the sponsor should be allowed a chance to answer the question. But our understanding is that there were some slight differences, especially for study number 3, where there were some quality control issues with biopsy in terms of its shipping to a central processing lab and use of it subsequently for analyses.

In terms of the actual protocol, there are no significant differences. The endpoints were similar in terms of the PCR, western blot, and immunofluorescence. But I wonder if the sponsor would like to add on to that.

DR. FUCHS: Thank you for the question. I think the original answer was a good answer in that there are some sampling differences in the studies. Study 3 had the poorest quality. It was the most

multi-centered study. And you see the prevalence of available biopsy is the lowest.

Another thing to point out is that the sampling that's done here is predominately of the same muscle group, tibialis anterior. We have no idea how drisapersen delivery to different muscle groups and different parts of the lower extremities varies. In preclinical studies, it varies quite a bit. So we don't even know that the muscle group that we're sampling necessarily represents the best sampling group.

Our conclusions is that there is pharmacologic evidence of activity. We have no intention of validating the dystrophin measures that we've made so far as a surrogate marker; rather, this is a good tool to verify quantitative delivery of drisapersen, its effect at the pre-mRNA level, and its effect on improving dystrophin, at least in a muscle group that we've sampled.

DR. ALEXANDER: Thank you.

Dr. Romitti?

DR. ROMITTI: Yes. This is for Dr. Tandon,

and I just have a couple of clarifications that I'd like on the matching study between placebo patients from study 3 and the historical control study. This is slide 31.

So just to be clear, it's really about the design, not about the results. You present the different rise time strata that you used for matching, but I was unclear about which strata you used to match on 6-minute walk distance and also age. So at what level of matching did you do?

DR. TANDON: Age is plotted on the X-axis. So the patient -- like a 9-year-old patient would begin where the 9-year-old starts and would continue --

DR. ROMITTI: So you matched by birth year, by year?

DR. TANDON: By year.

DR. ROMITTI: And for the walk distance?

DR. TANDON: And same thing for the walk distance. Walk distance is on the Y-axis. So the subject would fall where the baseline walk distance is on the curve, and would begin there.

DR. ROMITTI: I'm just trying to understand the strata because you have such small numbers here. Did you look for exact walk distance and exact age?

DR. TANDON: I can let Dr. Bhattaram, who did the pharmacometric analysis, elaborate more on this.

DR. BHATTARAM: I am Dr. Bhattaram from the Division of Pharmacometrics, OCP. So the graph that is being shown here on the X-axis is the age of the patient, and then the Y-axis is the 6-minute walk distance.

So what we did there is to overlay the progression in the 6-minute walk distance from the placebo groups from the three studies. So we're not exactly matching the 6-minute walk distance by a particular distance.

It is just showing, for example, if you have a patient who's starting at 400 meters in these 12 patients, and when you look at the patients in the placebo group comparatively, how do they land in the whole data?

DR. ALEXANDER: Dr. Farkas?

DR. FARKAS: Thanks. I think part of the question about matching is that we couldn't find matches in the entire placebo -- all the placebo patients. We couldn't find patients that had such well-preserved function.

So actually what we were trying to show here is even though the open label patients had this more preserved function at baseline, which predicts better function over the long term, that they were more or less -- again, more or less -- similar to the patients who you would think would decline more that were in the placebo arms.

DR. ALEXANDER: Thank you.

Dr. Zivin?

DR. ZIVIN: I'd like to know if any of the side effects were irreversible.

DR. TANDON: Dr. Mentari?

DR. MENTARI: In terms of the major --

DR. ALEXANDER: Could you introduce yourself, please?

DR. MENTARI: Sure. Sorry. I'm Evelyn

Mentari, and I'm the safety reviewer at FDA.

In terms of the side effects that were irreversible, we had a proportion of injection site reactions that were not resolved at the end of studies. In addition, we have the case of intracranial venous sinus thrombosis, as previously mentioned, which had the sequela of cranial nerve paralysis, which was not resolved.

DR. ALEXANDER: Thank you.

Dr. Gonzales? I'm sorry. Was there an additional comment? Yes. Dr. Farkas?

DR. FARKAS: I think that, again, I know this is clarifying questions, and I think we hope to discuss later this afternoon. I think part of what came out in the question and what came out in the answers is kind of an oversimplification, and what we'll like to discuss this afternoon is the fact that we're concerned about mortality. And of course, that's not reversible.

DR. ALEXANDER: Dr. Gonzales?

DR. GONZALES: This question is for Dr. Tandon, and it's relevant to the lower CK

values on slide 46. Did anyone look at an association of lowered CK values with any of the other timed assessments?

DR. TANDON: No. I did not do that. That's a good idea, but I have not done that.

DR. GONZALES: Thank you.

DR. ALEXANDER: Dr. Onyike?

DR. ONYIKE: Yes. My questions go to Dr. Tandon and Mentari.

Did you by perchance look at the treatment response differences in people with adverse skin reactions versus those without, as a measure of partial unmasking?

DR. ALEXANDER: So the question was for who?

DR. ONYIKE: Tandon and Mentari.

DR. ALEXANDER: Thank you. It was about skin reactions and --

DR. ONYIKE: Well, I'll repeat it, if I may. The skin reactions were common enough to have potentially unmasked subjects. And so my question is whether you noticed differences in treatment response for those with skin reactions versus those

without.

DR. TANDON: I think it varied across studies. I don't recall for each study, but I think some looked better and some didn't. I think it varied across studies. There was no consistent trend that subjects who had injection site reaction did worse on 6-minute, but I don't recall which study did that.

DR. ALEXANDER: Well, one might expect if they were unmasked, that they would do better. I guess the question is, were there any systematic analyses looking at the magnitude of the effect, stratified by whether or not a skin reaction was present?

DR. TANDON: There was no consistent affect. Like I said, the magnitude of effect, there was no consistency amongst the three studies.

DR. FARKAS: Again -- this is Ron Farkas. Maybe this is a matter for discussion this afternoon. But part of what's being asked is, is there any effect discernible when the total effect that you're looking at is very small? So looking

for correlations.

So if there's a 10-meter difference and then you start taking that apart, looking in a great deal of noise in the endpoint, and then start looking for correlations -- again perhaps a discussion for this afternoon -- but you're underpowered to find the difference between the different patient groups.

DR. ALEXANDER: Thank you. We're just about at the close of this section, but we will have time for more questions as well.

Mr. Cassidy, did you want to make a final question or comment?

MR. CASSIDY: In January 2015, BioMarin was told by the FDA that matching natural history data only with age and the 6-minute walk test would not be adequate in an NDA. "Additional data, such as ability to jump and hop and detailed history of corticosteroid use, would be necessary."

As of the date of the submission of the NDA application, the CINRG natural history data that was promised was not submitted. Has the FDA yet

received the CINRG natural history data?

DR. TANDON: The answer is no.

DR. ALEXANDER: Thank you.

We can extend the discussion for about 10 minutes, and we'll just shorten lunch by that amount. So let's take 10 additional minutes, and at this time if there are clarifying questions for either the sponsor or the FDA, that would be fine. And we'll go to Dr. Onyike.

DR. ONYIKE: Yes. This question is for the sponsor, and it regards dystrophin. One of the premises for the study is that there will be a change in the dystrophin levels. What I want to know is about the preclinical data.

Do you have thresholds for dystrophin expression that would essentially buttress the biological plausibility argument?

DR. FUCHS: We do not have thresholds that could suggest that it could be useful or interpretable yet as a biomarker of treatment benefit, as Dr. McDonald introduced.

We simply can look at mean percent changes

from baseline in individual patients and then summarize those, not in a categorical analysis but in a group comparison analysis, and observe pretty consistent findings across all three studies, which is amazing in the challenge of obtaining samples from these boys on a repeated basis and then reducing that to laboratory findings.

If you'd like, I could show you some of the data across all three studies. But in the interest of keeping it short, I'll turn it back to the chairman.

DR. ALEXANDER: Yes. Thank you. Well, I was going to ask as well about dystrophin because I'm having a hard time wrapping my head around it. I appreciate the arguments and belief and agreement, it sounds like, that it's not a suitable surrogate. On the other hand, it seems only plausible that one would expect increases in the production of this, if this is the purported mechanism of action of the product.

So I wondered if it's thought that the product has immunomodulatory effects that are

independent of dystrophin production, and how we should interpret the fact that, if understood correctly, the dystrophin increases is less than a third of 1 percent of baseline levels.

DR. FUCHS: Yes. I would remind that those percentage changes are in tibialis anterior, and we really don't know how to relate quantitative changes in dystrophin measured immunofluorescently. The protein is very complex and has a lot of functions. So again, at this point we considered a pharmacologic marker of activity.

The product, as you've seen from preclinical studies and clinical studies, appears to be more inflammatory than anti-inflammatory. So we don't really believe that there's evidence of its activity through an anti-inflammatory mechanism.

I want to be very clear that this product is intended to be used explicitly for patients who have exon 51-amenable mutations. It would be entirely another research undertaking to assess whether it had activity, and we do not intend to do that because we believe that it works by skipping

exon 51 in exon 51-amenable patients.

DR. ALEXANDER: Thank you.

Dr. Estrella?

DR. ESTRELLA: I have a question I think probably directed to Dr. Campion from the sponsors. There was a note in the presentation about alpha-1-microglobulin, which is thought to be a marker of proximal tubular dysfunction, and that they noted that this may be due to metabolism of the drug rather than actual injury.

I was wondering if there were additional biomarkers measured to corroborate this argument, or if there were other preclinical trials to support that.

DR. FUCHS: I'm sorry. Was that directed to the sponsor?

DR. ESTRELLA: Yes.

DR. FUCHS: Yes. I'm going to ask Dr. Portale, who's our consulting nephrologist, to come and speak to alpha-1-microglobulin.

DR. PORTALE: Good morning. My name is Anthony Portale. I'm a professor of pediatrics and

chief of pediatric nephrology at the University of California San Francisco. I receive compensation from BioMarin as a consultant, but I have no financial interest in today's proceedings.

The question was regarding whether we had the mechanism of the low molecular weight proteinuria? Was that one of your questions?

Well, low molecular weight proteins are reabsorbed by the proximal tubule bioreceptor-mediated mechanism, and they appear in the lysosomes of the proximal tubule. Oligonucleotides like drisapersen appear in the same location, and we understand that they are resorbed also.

There's preliminary experimental data that show that not only is drisapersen or oligonucleotides like drisapersen reabsorbed by the proximal tubule, but they also impair the reabsorption of other proteins like alpha-1-microglobulin and albumin. So we understand the increase in low molecular weight proteinuria to be an interference with the normal reabsorptive process rather than a tubular toxicity.

With respect to damage to the kidney, we do not see Fanconi syndrome. We do not see glucosuria. We do not see hypophosphatemia or hypokalemia. So there's no generalized tubular toxicity. The low molecular weight proteinuria does increase, but it's non-progressive and it's reversible. The total increase in urinary protein is very modest, and it is not progressive, either.

DR. ALEXANDER: Thank you.

Dr. Nuckolls?

DR. NUCKOLLS: This is a question for the sponsor. Is there any data on possible immune response to the dystrophin in the treated patients?

DR. FUCHS: I'm going to have Dr. Schweighardt come and speak to antibody responses, and she can speak to dystrophin, drisapersen. But I think your question was directed to the dystrophin that's made? Okay.

DR. SCHWEIGHARDT: I'm Becky Schweighardt. I am the head of immunogenicity assessment at BioMarin. And we looked for antibodies against drisapersen -- sorry, against dystrophin -- also

dystrophin -- and we found that there were 2.6 percent of the patients that developed an antibody response against dystrophin. But we found a similar amount in the placebo subjects as well, so we feel it's a background.

DR. NUCKOLLS: And did you look for circulating T cells?

DR. SCHWEIGHARDT: No. We did not look for T cells against dystrophin. We think because most of these patients have revertant fibers that they have a natural immune tolerance against the shorter protein.

DR. ALEXANDER: Thank you.

Dr. Kesselheim?

DR. KESSELHEIM: This question goes back to the original presentation. I was wondering, in addition to looking at the blinding, whether or not any assessments were made of the patients to assess whether they thought they were in the placebo or the treated group as another mechanism of assessing blinding and unblinding.

DR. FUCHS: I don't believe that was

undertaken. We do have the data that looked at injection site reaction, yes. And I wonder, Mr. Chairman, if you'd like -- Dr. Chairman -- if you'd like us to look at that data.

DR. ALEXANDER: Sure, briefly.

DR. FUCHS: Yes. So slide 1 up. We classified patients as to whether they did or didn't have an injection site reaction in the drisapersen group in the three studies. And apologies, these are listed as their original study names, so this is study 3, 1, 2, in that sequence.

For example, in study 3, 89 patients had an injection site reaction in the drisapersen group versus 28 in the drisapersen [sic] group. The mean change from baseline 6-minute walk distance was actually adverse relative to the patients who didn't have injection site reactions. I think you'd expect the opposite.

Study 117 or study 1, with the best treatment result, was only a 4-meter favorable difference in the patients who had injection site reactions. And in study 2, there was a

substantially favorable improvement in 6-minute walk distance in the un-injection site reaction group.

Again, I can offer Dr. Wagner to speak to study conduct issues. But in sum, we believe that there was a comprehensive program to prevent this problem, and there's no quantitative evidence that this occurred.

I'll defer to the chairman as to whether you want to hear more about this in particular.

DR. ALEXANDER: No, I think that's okay. But thank you. That was helpful.

Dr. Romitti?

DR. ROMITTI: This question is for the sponsor. I have a question about loading dose and hearing the recommendation for a loading dose. And I'm just wondering, with the differences in study participants and the information that's been provided, how the study 3 differs and are probably less functioning patients than study 1 or 2.

Given study 1 had higher functioning patients to study, does the sponsor have evidence

that a loading dose would be effective for lower functioning patients?

DR. FUCHS: We've looked at tissue concentrations versus baseline walk, and there does appear to be a trend that in patients who have adverse tissue concentrations, in the absence of a loading dose, get to lower levels. And my team is looking for the data.

We haven't compared the loading dose explicitly in the patients who got the intermittent regimen according to their baseline walk levels, I don't believe. We'll have to look for that, and if of interest, we can come back to it.

The primary learning has been that as muscle impairment advances, it's harder to get drisapersen into the muscle tissue. And so it makes sense that a loading dose -- and the only question I have about study 1 -- if I could have slide 3 up just to quickly show it to you.

This is in study 3 without the loading dose. On the far right are the lowest quartile of baseline 6-minute walk distance, and on the left

two bars are the highest quartile, and then the intra-quartile range of baseline 6-minute walk distance. And you can see there's a trend.

Now, there's very much fewer patients in study 1 with the loading dose, and they were healthier. So I don't know if we would see the effect of the loading dose on delivery in the adverse population, but we do see it in the advanced population.

DR. ALEXANDER: Thank you very much.

At this point, we will break for lunch, and we will reconvene at 12:30 promptly. And participants are reminded to not discuss the contents of these proceedings during the break. Thank you very much.

(Whereupon, at 11:42 a.m., a luncheon recess was taken.)

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

(12:32 p.m.)

Open Public Hearing

DR. ALEXANDER: Thank you. I think we'll get started. I understand that the sponsor may want to respond to something that was discussed prior to the break, and I would just request that we hold off on that briefly, and we can do so after the open public hearing comments.

Both the Food and Drug Administration 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 public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial

information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at 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 this 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 on 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 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 myself, by the

chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CWIK: I am Valerie Cwik, and I am the chief medical and scientific officer for the Muscular Dystrophy Association. I have no personal relationship with the sponsor, but the Muscular Dystrophy Association does receive support from the sponsor.

Good afternoon. Thank you for allowing me to present my comments. This is a watershed moment. Today there are no disease-specific therapies for Duchenne muscular dystrophy, a disease that we have heard is 100 percent fatal.

Our community desperately needs and deserves treatment option, and every option that fits in the benefit/risk framework of the Duchenne population should be made available as quickly as possible.

I'm here to share MDA's perspective, which reflects 65 years of funding groundbreaking

research and clinical care in more than 180 clinics nationwide. But I also come before you as a clinician, a neurologist who has dedicated my career to helping those living with Duchenne and other neuromuscular diseases.

I've seen firsthand the devastating impact of this disease on those who live with DMD and those who love them. As I look back on the first patient I cared for with Duchenne, I'm reminded that my 25 years of medical practice in this field is about the same amount of time that the average person diagnosed with Duchenne can expect to survive.

However, my message today is not about the devastating nature of Duchenne, but of hope and optimism. We have seen improvements resulting from multidisciplinary care provided in our clinics. MDA's database of 7700 boys and men with Duchenne in the U.S. shows the proportion of individuals living with DMD has trended upward in age over the past 15 years.

While this is a promising development, it is

not enough. We cannot and will not move the needle without safe and effective new therapies. And we need them quickly, as our community does not have the luxury of time.

For 65 years, MDA has supported the foundational research that many of today's advances are built on. MDA has invested more than $230 million for Duchenne-specific projects, with a 20-year investment in exon skipping research.

The exon skipping approach is meritorious. Dr. Lou Kunkel, one of the most notable leaders in the scientific community on this disease and a member of our board of directors, has said, "I see exon skipping as one of the promising approaches being developed for DMD, and wholeheartedly support it moving forward."

While not a cure, exon skipping drugs could meaningfully slow disease progression. Abilities such as to physically adjust into a more comfortable position independently, to operate a joystick on an electric wheelchair, and to simply be able to hug the people you love, are typically

not captured in clinical trials. But that does not diminish their importance to those who will lose or have already lost them.

MDA is determined to change the status quo and bring safe and effective treatment options to those we serve as quickly as possible. Before you today is the first disease-specific therapy for Duchenne under consideration for approval by the FDA.

We know that the FDA and this committee will exercise its due diligence in considering drisapersen, and MDA and our supporters are hopeful that if found to be safe and effective, it will become the first of many therapies approved to combat Duchenne muscular dystrophy. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. MUSKOPF: Hello. I am Erica Muskopf, and my 11-year-old son Brody has Duchenne. Our

travel was provided by CureDuchenne and the EveryLife Foundation.

We are here to step through a doorway into a world of possibilities, options, discussions, treatments, and hope for my son Brody and this community. When Brody was born and diagnosed with DMD, I was read the final chapter of the story of his life that hadn't even begun. I am here to share the before and after of drisapersen that hasn't been provided to you in the data.

At 7 years old, Brody began to receive drisapersen. Before this drug, he couldn't climb the stairs with alternating feet, jump on one foot, or get up without at least a partial or full Gowers, depending on fatigue.

After a few months on drisapersen, things began to change. He climbed up stairs, alternating feet without using handrails. He was running and jumping while clearing the floor with both feet. He also had a lot more energy. And, well, his Gowers turned into this. And I have a video. And this is not the same child that you saw earlier,

but they look alike.

Over time, he actually almost looked normal, even though we learned afterwards he was only on a 3 milligram dose. I was not going to believe in drisapersen and get my hopes up just to be disappointed, and my husband was the biggest skeptic of all. One person after another commented on how different he was, and we could no longer ignore the considerable improvement.

For the first time, we had real hope. Unfortunately, with that excitement came great disappointment. We had to go off the drug over a year, which led to a devastating loss of function.

While waiting to restart, Brody was barely able to get up off the floor using both hands and all of his strength. He could not jump, climb stairs, get into the car by himself, and his energy plummeted. He was falling about three times a day. He was trying so hard to be normal, and my heart broke watching his rapid decline.

Now that he has been back on drug for a little over a year, Brody has begun to see some

benefits once again. But they look different this time. He has gone almost 2 months without a fall. He has more energy, and his pulmonary function tests are higher than they've ever been in his life. At the rate he was declining, his doctors and I expected him to already be non-ambulatory, and he is still walking.

We have seen different gains at different ages with this drug. We have experienced some of the side effects of the drug, which we have not considered serious. Brody had protein in his urine, site reactions, and the injection was painful. We're looking forward to beginning of infusions next month.

We have also experienced the side effects of Duchenne, which is watching my son lose function and die a little more each day, knowing that one day he will take his last breath in my arms. The data on that is indisputable and will happen with 100 percent accuracy.

Our children are fighting for their lives, and they deserve therapies that can change their

quality of life and the outcome of this disease. This should be the day that the ending of this tragic story is rewritten. Please approve this drug.

Thank you for the opportunity to share our story and for your time and consideration of approving drisapersen.

DR. ALEXANDER: Thank you very much.

Will speaker number 3 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. GONZALES: Good afternoon. My name is Michelle Gonzales. My son Nicholas has Duchenne muscular dystrophy, which is a progressive disease, and he's 13 years old. As a disclosure, our travel was provided by CureDuchenne and EveryLife Foundation.

Nicholas was diagnosed just before his fifth birthday. We had waited over 3 years for drisapersen to begin trials here in the United States, and Nicholas had just turned 9 when he

started in the trial. The trial was double-blind and lasted 48 weeks, and at the conclusion, we were informed that Nicholas was on placebo. Although disheartening, we understood the necessary of having a placebo study.

We were told that Nicholas would be part of an extended study and would be receiving the drug. Nicholas started weekly injections of 6 milligrams per kilogram of drisapersen, and it lasted until week 12 before the extended study had halted for just over a year. When the redosing extension study began, Nicholas was 12 years old, and has been receiving weekly injections for now 56 weeks.

Nicholas wasn't sure himself that he wanted to continue in the trial. He decided to meet with his doctors in Cincinnati, and they discussed the drug and its intention, including benefits versus risks, with him. They also discussed how our boys only need 5 percent of dystrophin in order to continue to apartment walk. Nicholas made his own decision to continue with the trial. He understood the importance of preservation of his remaining

dystrophin.

Just recently Nicholas was sitting on the floor in his bedroom playing, and I had to run out for a few minutes. And when I returned, he was sitting on the couch. He said that he was able to get up from the floor using furniture. Before this time, Nicholas had depended on me to help him up from the floor, as it's extremely difficult for him to get up by himself.

I am amazed that he is still able to walk short distances, is independent as far as dressing himself, bathing himself, toileting, eating, drinking, and he can still throw his arms around me to give me a hug.

I believe if he wasn't on drisapersen, he would have lost his ability to walk, and that his upper body strength would have deteriorated much more rapidly. I have known boys who have received absolutely no treatment, and they stop walking permanently at age 9, and have lost upper body strength by 12 to 13.

Nicholas is 13 years old, and as you can

see, he's still able to walk and maneuver his arms and his upper body without much difference from a year ago. In fact, his 6-minute walk test had increased by 21 meters from week 24 to week 48 of the extension study, and we're only going into week 60.

We understand that our boys will require a combination of therapies to treat Duchenne. This is one piece of that puzzle that can begin the process of treatment.

I would like to see this drug succeed because I would like to see my son have a fighting chance to continue to do everything and the everyday tasks that we all take for granted. I want Nicholas to continue to be as independent as possible because he deserves it. And all of our children with Duchenne deserve a treatment to slow the progression of this disease until we can find a cure. And this treatment has shown to me that it works. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 4 step to the podium and

introduce yourself? Please state your name and any organization you are representing for the record.

DR. RUPP: Thank you for the opportunity to speak today. My name is Dr. Tracy Rupp. I was previously a clinical pharmacist and pediatric nutritionist at Duke University Medical Center, and am now a senior fellow at the National Center for Health Research.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy-makers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

We strongly support a drug regulatory process that gets safe and effective new treatments to patients as quickly as possible, and patients with Duchenne muscular dystrophy don't have time to spare. This is a devastating condition that usually leaves young boys wheelchair bound by their teens and facing the end of life at a time when other young men are entering the prime of their

lives.

For a disease with no cures and with such catastrophic consequences, we understand that patients are often willing to accept treatments that carry more risk. However, to be able to accept a drug with risky side effects, we must have good evidence that the drug is effective.

Unfortunately, we don't have substantial evidence that drisapersen is effective, but we do have evidence that the drug has life-threatening side effects. We do not recommend approval of drisapersen because we cannot say it has a favorable risk/benefit profile.

Drisapersen was thought to exert its beneficial effects by increasing levels of dystrophin. However, a number of biomarker studies found that drisapersen does not significantly increase dystrophin levels beyond those of untreated patients. Similarly, the large phase 3 trial did not find convincing evidence that the drug was effective at increasing the distance participants could walk in 6 minutes.

The sponsor argues that a post hoc subgroup analysis shows the drug is effective in younger boys with a 6-minute walk distance of less than or equal to 330 meters. But as we heard earlier, this analysis is no longer statistically significant if one of the patients is removed from the analysis.

This placebo patient was no longer able to participate, so his values were entered as zeroes, thus making the results more favorable for drisapersen. This type of analysis can only be said to be hypothesis-generating. This hypothesis must be trusted in a double-blind, randomized, placebo-controlled trial of sufficient size to know whether it is actually true.

Not only is the drug ineffective, but it's also unsafe. Drisapersen has life-threatening side effects, including the potential to cause platelet counts so low that fatal, spontaneous brain or lung hemorrhage could occur. It also causes kidney, skin, and vascular damage.

Studies indicate the risk of adverse effects may increase with time and cannot be completely

prevented with close monitoring. This is very concerning for drisapersen since patients would require lifelong therapy.

In conclusion, we are deeply disappointed that drisapersen is neither safe nor effective. Patients and their caregivers have literally invested their lives in the hope that this drug would have a profound impact. But patients with Duchenne deserve much more than false hope. They deserve safe and effective treatments.

Of course, there are some patients for whom drisapersen may have been effective, but they are the exception rather than the rule. We urge the drug sponsor and the FDA to make drisapersen available to these patients through the compassionate use program, as appropriate, while continuing to collect information on the drug's safety and efficacy.

Thank you for the opportunity to comment today.

DR. ALEXANDER: Thank you very much.

Will speaker number 5 step up to the podium

and introduce yourself? Please state your name and any organization you are representing for the record.

MS. ROTHE: My name is Jessica Rothe, and lodging provided by CureDuchenne.

I am here today for my son, who lives with Duchenne muscular dystrophy. Although my son is not in the drisapersen trial, his mutation is in the pipeline of compounds to be developed. My family and I have watched and celebrated our friends' sons who are in the trial who have gained skills that they did not have before.

Examples of this are new abilities to climb stairs, climb in cars, and ride bikes. Although these abilities seem like commonplace and are activities that most of us take for granted, this change is very significant for children with Duchenne. The inability to do everyday activities requiring even moderate strength and endurance isolates our boys from their peers and their community.

These new abilities show a sign of improved

muscle integrity and significantly enhances the quality of life for these boys. On one hand, we are very excited for these boys, who are getting better without a doubt. It is also very difficult to see these gains be just out of reach for our family.

After seeing a video of a boy jumping into his car, my son said, "Wow! I wish I could do that." I couldn't agree with him more. And it would be a dream come true for him to be able to ride a bike.

I have been following this drug for many years and have been encouraged by the data. We have heard for some time that the exon my son needs will be worked on once the first one is approved. We have made an effort to be very careful with our son in hopes that he would still be walking when his turn comes to access this drug.

We know the drug works best when there is muscle to rescue. My son is now 13, and I fear that his window is closing. So we are anxiously awaiting a favorable outcome so that the drug

company can start development on the rarer exons like ours as soon as possible.

Although today we are focused on approving a drug that skips exon 51, I think it's imperative to mention the need for a path forward that allows many more boys to benefit from this life-changing drug. The videos I have seen of the boys who have been on drisapersen gives me hope for a better life for my son.

I am also encouraged by the long-term data from the boys who have been on the drug 6 years who are getting better in their walk times. It is my belief that this drug is a game-changer, and the time is now for approval.

This decision will alter the course of the lives of the boys and their families. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 6 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. TABORSKI: My name is Denise Taborski. My son Braden is 9 years old. He was diagnosed

with Duchenne in 2010. I had never heard of Duchenne, but I very quickly realized how hopeless the diagnosis is. There are no treatment options available. So when he was offered a chance to enroll in a phase 2 clinical trial for drisapersen in 2012, we jumped at the chance.

He was on the drug for 6 months, and although the progression of the disease may have been slowed, he experienced several side effects, with proteinuria being the most concerning. Several injections were withheld throughout the time he was receiving the drug. Thankfully, he was being monitored as part of the study, so we were able to know how his kidneys were being affected.

Earlier this year, when he was offered a chance to continue in an extension of that trial, we declined. His quality of living is more important to us than constantly worrying about how toxic a drug may be to him.

Braden is now receiving a different exon skipping drug as part of another clinical trial. I consider us very fortunate to have had the

opportunity to experience both exon skipping drugs. I can make an informed decision on which drug is the best fit for my son.

We all agree that we need options. What works best for my son may not be the best choice for another. Duchenne is a desperate diagnosis. With all of the new treatments on the horizon, we need to evaluate what is an acceptable risk for our own child.

Most importantly, we must remember to not sacrifice the safety of our boys to the desperation of the disease. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 7 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. DIVIN: Good afternoon. My name is Jessica Divin, and I'm here today with my son Ben, who has Duchenne muscular dystrophy, to share our story. Our travel and accommodations were provided by CureDuchenne and EveryLife Foundation.

Ben is approaching his 10th birthday in

January, but he was 5 years old when he first entered the drisapersen clinical trial. At the end of 24 weeks, we were seeing some improvement, such as alternating feet while climbing stairs, riding a bike, and less fatigue.

At the end of the study, we were told Ben had been dosed with the lower cohort of the drug. Since we felt we had seen a response at the lower cohort, we were very excited for him to redose at the full amount of 6 milligrams per kilogram. After waiting an entire year without treatment, he was given that chance. However, our hope was short-lived when after only 11 doses, GSK walked away from the study.

Yet another year passed and Ben was dosed for the third time. During breaks from dosing, Ben continued to follow the normal trajectory of Duchenne and began showing decline in function. Since we had no other options, we were forced to increase his steroid dosage. We did so twice.

However, our real story begins in March of this year, at 20 weeks of redosing. Ben was

fishing with his grandfather when he tripped over a rock and suffered a spiral tibia fracture and broken fibula in his left leg. We were devastated, knowing the ramifications of a broken leg for a child with Duchenne.

Due to the nature and the location of the break, it could not be fixed internally, and we had to cast. For six weeks, Ben could not bear any weight on his left leg. Simple tasks we had taken for granted, like walking to the dinner table, getting out of bed, and attending to his own bathroom needs, had become impossible.

After Ben began to heal, we took him to his physical therapist. She was upfront with us and confirmed our fears that due to the long time period without ambulation, there was a chance that he could have permanently lost function. However, as you see today, he is standing with me, walking unassisted. We feel that his level of recovery might not have been possible without treatment through exon skipping.

There are several major things we have seen

since the recovery of his broken leg that has convinced us that drisapersen is making a difference in Ben's day-to-day life. First, Ben is walking distances we feared would never again be possible. A few examples are walking around the home, within school, church, from the car and the places such as movie theaters and restaurants, as well as in and around his Cub Scout meetings. He often chooses to have his wheelchair remain in the car.

He has also maintained the ability to rise from the floor unassisted, and Ben is still performing tasks that allow him to maintain independence. The greatest of these occurred a few weeks ago in our home, when he walked down steps to the garage to get in the van and buckle himself. Imagine our surprise when we found him sitting in the van waiting on the rest of us.

Maintaining some degree of independence has been huge not only physically but also emotionally. And perhaps these examples seem insignificant to most, but I cannot stress enough how monumental and

meaningful they have been to Ben and to our family.

Overall, we believe that exon skipping is a viable option for the treatment of Duchenne. The side effects, which include pain and injection site reactions, are unfortunate. However, we still believe that exon skipping is the reason Ben was able to maintain his level of ambulation following the fracture.

After what we saw with Ben regarding stability and regaining mobility, we feel that drisapersen would also preserve his upper body strength. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 8 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CLEARY: Good afternoon. We are Simon Hogue, 15, and Andrea Cleary from Montreal, Canada. Our expenses have graciously been covered by CureDuchenne and the EveryLife Foundation. If you could play the video on mute, please.

(Video played.)

Simon was finally diagnosed at the age of 6, but we definitely knew that there was something wrong by the age of 3. His knees were constantly shredded from falling, and he had even knocked his front teeth loose and needed stitches. As parents, we slowly came to accept all that Duchenne would entail. And then that fateful call came when he was 11.

We read the consent form and the possible side effects carefully. Being a disease of unmet need, we felt that the possible benefits were worth the risks, and that has held true to this day.

Simon began weekly injections in September. By Christmastime, little hints of benefit began appearing, at first, just an increase in energy, less fatigue. Then he began to alternate feet when ascending our stairs and didn't need a rest halfway up any more.

Soon enough, he was breaking out into fits of spontaneous random dancing, something he had never been able to do before. It was the Duchenne equivalent of Riverdance in our house. And I could

not believe my eyes the first day I saw Simon skipping and galloping merrily down our hallway, feet clearing the ground.

I waited for that sound that all Duchenne parents come to dread, that sickening thud when your child's legs simply crumple beneath them. Well, that sound became a thing of the past for Simon during treatment.

His balance improved so much that he regained the able to ride a two-wheeler without training wheels, something he had lost months before the trial. He was playing 25-minute dodgeball games at Scouts. And while such behavior is frowned upon, Simon was able to punch and kick much faster and harder in his daily wrestling bouts with his brother, holding his own for the first time in his life.

Simon received drisapersen for two solid years, until the halt in September 2013 at the age of 13. As you can see from the videos I submitted, this drug was a major benefit to Simon. Children with DMD don't just gain abilities like this

without drugs such as this. This cannot simply be wishful thinking or placebo effect. My son lives the results.

While still fully ambulatory at the age of 15 and a half and fiercely independent, his disease did progress during the halt. We were glad to redose this past summer.

Please approve drisapersen and other effective drugs in the fight against Duchenne. The kids can't and shouldn't have to wait.

MR. HOGUE: Good afternoon. I'm Simon. I feel better when I take drisapersen. I can control my body and do more of the things I want to do. I can look after myself. I shower and wash my hair by myself. I can cook great meals. I can even do my own laundry if I have to.

I don't use my wheelchair or scooter at school. I just walk around like the other kids. I walk back and forth two blocks to the bus stop. The injection site reactions don't bother me too much. I used to have bruises and scrapes all over, so what's the difference? When I go to the pool, I

just wear a water shirt so nobody can stare.

Please approve drisapersen so that other kids can feel better, too. Thank you.

DR. ALEXANDER: Thank you very much.

Speakers 9 and 10 are no longer planning to speak, so we'll more to speaker 11. Will speaker number 11 come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GULATI: My name is Dr. Neera Gulati, and I'm reading Laurie Burrack's statement.

"My oldest son William was born in 1999, his brother Isaac was born in 2001, and during their early childhood, everything was normal. As they grew older, we began to see that they were not able to keep up with their peers and that they struggled to run and jump.

"After several tests and trips to specialists, a diagnosis of Duchenne muscular dystrophy was made, and our family was devastated by the prognosis. I began to search the web looking for treatment to save my boys, and found

very little hope.

"Our neurologist told me of a new treatment that was being developed called exon skipping, and he believed it was very promising but also years away from trial. He stated it could be 8 to 10 years before we could possibly try this treatment. My sons were 6 and 3 at that time, and I remember thinking that time was not on our side and that it would come too late.

"As time went by we did everything we could to slow the progression of Duchenne while waiting for this treatment. But this condition is relenting and decline is inevitable. Walking became more difficult, and William began using a wheelchair for long distances.

"Personal care attendants were hired to assist with personal cares and bathing. Falls became more frequent and getting up more difficult, sometimes requiring a gait belt. The boys became physically tired, often too tired to complete homework at the end of the school day.

"In April of 2012, my boys were finally able

to start the drisapersen clinical trial. They were 13 and 10. As weekly dosing continued, we began to see subtle but significant changes in our oldest boy. William began to spend his summer days outdoors, building forts and exploring, and he had more endurance and did not get tired.

"In August of that year, I took my boys to the fair and brought the wheelchair to push William to various rides and exhibits. We spent several hours going from ride to ride and walked miles with me pushing an empty wheelchair as he walked and even ran to each ride, and he got on the rides without assistance.

"Trips to the grocery store changed as well. Instead of William using the wheelchair, he began to walk through the store without assistance. Instead of riding in his wheelchair, at times he would push his brother Isaac around the store in it.

"The falls declined and eventually stopped occurring for William while he was taking drisapersen. William no longer needed hands-on

assistance to bathe or dress. Other changes included softening of the calf muscles, less tension in the muscle, and reduction in restless leg pain.

"His social interactions improved, and he began to speak more at school. His grades improved, and the math that he struggled with became easier for him. The only side effects during this time were injection site pain and redness. No other problems occurred while receiving drisapersen.

"After the study ended in 2013, we learned that William had received drisapersen at the highest dose throughout the study. Our other son, Isaac, had been on placebo. The improvements in William were maintained for about 6 months after completion of the study.

"In time, both boys began to need more assistance with personal care, such as bathing and dressing. Assistance with getting up from a chair and lifting them up after a fall was again needed.

"In April of 2015, at the ages of 16 and 13,

both boys started dosing with drisapersen, the extension study. William and Isaac recently completed 6 months of weekly injections of drisapersen.

"Both boys have had an increase in stamina and independence. Isaac no longer needs help to put on his shoes or get up from a chair. William is now able to complete his own shower and dress himself without assistance, and we no longer hire personal care attendants.

"William was able to take his driver's training requirements this summer, something he could not do last year due to fatigue. He's now a licensed driver after passing his driver's test using my van with no adaptations.

"My youngest son Isaac has been able to help with the farm work and has learned to use some of the equipment, and is able to do woodworking that he loves. Both William and Isaac are still walking and doing well."

DR. ALEXANDER: Thank you very much.

Will speaker number 12 step to the podium

and introduce yourself? Please state your name and any organization you are representing for the record.

MR. PENNER: My name is Cam Penner. My travel arrangements have been provided by CureDuchenne and EveryLife Foundation. My 13-year-old son Doug has DMD. Our journey with drisapersen began in the summer of 2011, just before his 9th birthday.

Doug was just beginning his DMD decline. He had recently lost the ability to get air under his feet when he jumped. When he climbed stairs, he could alternate feet at the beginning of the day but not at the end. His walking distance was in decline as well.

Over the course of the first year on the drug, we saw a complete halt to his skill loss and a noticeable improvement in his balance and endurance. He was faster and more confident on the stairs and regained the ability to alternate feet going up, even at the end of the day.

By the end of his third year, we could see

unmistakable gains. He learned to ride a kick scooter and glide balanced on one foot for 30 seconds at a time. I watched him walk up a dozen concrete stairs with no hand rail or help, alternating feet.

He was even suggesting taking evening walks as a family. One night I tracked our progress with my GPS. We covered 2.6 miles in 65 minutes. The route had 240 feet of elevation gain on it, and he was not even tired until two-thirds of the way through, although I certainly was.

The week of his 11th birthday, Doug went on a hike with his class. Over the next 2 to 3 hours, he hiked a 3.7-mile trail, and he was quite tired by the end. But after just 30 minutes of rest, he was back up and running, playing capture the flag in the field. I'm not surprised that the 6-minute walk test didn't capture these improvements. Balance and endurance are what we're seeing, and they're making his life so much better.

Then the study was halted. For 18 months, we anguished over whether it would restart. We

watched Doug's decline resume. Amongst other things, he once again lost his ability to jump, his ability and desire to take walks, his ability to climb up the stairs at home and on the school bus. He just wanted to lie on the couch.

I can't even begin to describe the emotional toll watching this has taken on our family. To have something that a difference in everyday life taken away is devastating in ways that I can't put into words.

Six months ago, we restarted on drisapersen. Since that time, we have noticed once again the decline has been halted. He doesn't avoid the stairs the way he does before, and at the end of the day he's going up them, standing on his own. He is only alternating feet on a few stairs at a time right now, but he's showing promise.

Yes, there are side effects. Doug is one of the boys who experiences injection site reactions. Every injection is a painful one. Every time we talk to him about it, he feels that the benefits outweigh the side effects. I asked him last week

whether, given a time machine, he would go back and make a different decision about being on this drug. He gave it a second or two of thought before replying, "I would still do it."

As but a single person, Doug is not statistically significant. And I know that as a parent, science doesn't measure my testimony as especially reliable, but my son is a significant person, and his journey is a significant indicator of the effectiveness of drisapersen. And most of all, the benefits I have watched this drug bring have significantly improved his quality of life. Thank you for your time.

DR. ALEXANDER: Thank you very much.

Will speaker number 13 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. FURLONG: Thank you. I'm Pat Furlong, president of Parent Project Muscular Dystrophy. Parents and their sons carry the greatest risk. It's an honor and a privilege to be here today. I

have no financial disclosures to report, no investments in any company developing drugs of biologics for Duchenne, not personally or professionally.

Three and a half minutes is a very short time to discuss a lifetime of experience with Duchenne. During the last 30 years, I've met more than 5,000 families from around the world. Each has their own story, one of observing a delay in milestones that every parents wants and needs to see in their child as they grow, increasing concern about a child's tired legs or his struggles on steps, many of those same families an odyssey of diagnosis from months to years, when finally a physician in some small office mentions the word Duchenne and spreads the tarot cards predicting a future of decline and death.

Day by day, we watch as our children gain strength and mark those precious days, only to watch those milestones disappear: walking, lifting the arms to the face, breathing, and for some of us sitting here, watching them being lowered into the

ground.

My sons were diagnosed in 1984. They died at 15 and 17, just seven months to the day apart. At that time, individuals with Duchenne had no options. None. Each of us live with the words "if only" on a feedback loop, wishing for knowledge, understanding, options, and the ability to turn back time.

Duchenne has a perfect record of lives claimed. In an effort to understand the collective voice of the Duchenne community, PPMD conducted a pilot study to explore caregiver preferences, in this case parents, because we believe it's important to ensure regulatory agencies and advisory committees that they are well informed about the benefit/risk in Duchenne.

The study found that caregivers believed that they carried significant risk with the diagnosis, and they were willing to accept additional risk to achieve their highest priority, slowing disease progression. That is even beyond extending life by 2 to 5 years.

Clearly, all of us make benefit/risk decisions every day of our lives, when we drive a car, cross a street, or attend a concert in Paris. With the diagnosis of Duchenne, the decisions are daily. Parents identify clinicians that they trust who will be willing to guide them in making these decisions about benefit and risk and uncertainty. How many of us have ever asked the doctor, "Doctor, what would you do if this was your son?"

Today we're here to discuss drisapersen. The decision to recommend drisapersen is a monumental responsibility for all of us. You're hearing stories on both sides, from families who've seen positive changes in their son and from families who've made benefit/risk decisions that are different. Each of these families testifying today is an N equals 1 experience.

Today the community has had a comprehensive exposure to the data and a collective exposure to the patient experience. Every family must weigh benefit and risk in the context of their lives. Now we ask you today to carefully weigh the data,

consider the risks that we as families must carry, as you consider the potential benefits and risks of drisapersen.

As a community, we want and need safe and effective drugs. We are looking for options that provide meaningful benefit, more days to keep up with friends, more days to be independent, to walk up a step, and to breathe without the need for assist devices.

A recommendation of approval today would be a start, albeit with some caveats of limited use and safety concerns. But it is a starting point, one option that could certainly lead the way. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 14 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. CARLONE: My name is Tonya Carlone. This is my husband Anthony and my son Gavin. He will be 10 years old in March. Neither myself nor

my family has any financial interest in BioMarin. My family and I provided our own travel expenses from Seattle, Washington.

Gavin was diagnosed in November of 2007 at the age of 18 months. At the age of 5, Gavin participated in the drisapersen trial. Six months into the trial, Gavin started alternating his feet on stairs. This is something he had never been able to do before the trial. He started having more energy. He stopped complaining that his legs were hurting. His balance became more stable as the trial progressed.

After 48 weeks, we were unblinded, and we found out that Gavin had been on the full 6 milligram per kilogram dose of drisapersen. Gavin's North Star assessment at the start of the trial was 29 out of 34. At the time of the halt in September of 2013, Gavin's North Star had increased to 34 out of 34. He wasn't just stabilizing. He was improving.

We were devastated when drisapersen was halted and he was off for 16 months. Three to

4 months off medication, we started noticing his stamina diminishing. He'd been able to ride his bike to and from school. He started only being able to make it halfway.

Gavin said to me at this time, "Mommy, I want my shots again." He said, "I could run faster and I didn't feel as tired." We could visibly see him starting to decline. After 9 months off drug, Gavin's North Star decreased to 32 out of 34, and his Gower came back.

Eleven months ago, Gavin redosed onto drisapersen. He is now riding a larger, 16-inch bike. He is fully participating on his soccer team. His Gower is completely gone again, and his North Star assessment has gone back up to 34 out of 34 at almost 10 years of age. From the start of treatment at age 5 until now at almost 10 years of age, Gavin's 6-minute walk test has increased greater than 130 meters.

This past week we went to my daughter's volleyball practice. Gavin started throwing the football with another boy. As they were playing,

the other little boy's father said to me, "Wow, he's got an arm on him. I wish my son did. I think you may have a little quarterback on your hands." This is a man that I had never met before. He saw Gavin as a normal, healthy child, not a boy with Duchenne.

I had a cousin with Duchenne that passed away in 1989. Drisapersen has allowed Gavin to live a life of independence, mobility, and opportunity, a life that, sadly, my cousin wasn't able to experience. I will never forget when my mother and my aunt sat at our kitchen table crying as they listened to hymns to play at his funeral.

Drisapersen has dramatically altered Gavin's quality of life. Beyond a shadow of a doubt, the benefits far outweigh any possible risks. Gavin has not experienced injection site reactions. His protein urine levels were higher before starting drisapersen than they have ever been while on drisapersen.

Please give us a chance to change the outcome of Duchenne and help those waiting for

their turn. Thank you.

DR. ALEXANDER: Thank you.

Will speaker number 15 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. JURACK: Hello. My name is Karen Jurack, and I have no financial interest whatsoever in any exon 51 skipping drug. I am the mother of a son with Duchenne muscular dystrophy. He's 14 years old. His name is Joshua. And he has a deletion mutation in genes 49 and 50, which makes him a perfect candidate for an exon 51 skipping drug.

We've been battling this disease for the last 10 years, and we have seen firsthand, as many of these families have, the toll it takes on these boys' bodies. Especially in the last two years, we've really seen a decline in Joshua's mobility. He lost mobility a long time ago, but even in his arm strength and his neck strength, he's really losing a lot of that control.

He was diagnosed at age 4 and a half. He lost the ability to walk at age 9. And now in July of 2014, he had spinal fusion surgery, and that has precipitated his lack of arm strength. It's a catch-22. He needed the surgery to create the curvature of his spine from sitting in his wheelchair for so many years, and now we're battling the fact that he's lost the ability to feed himself. All those freedoms that you use your arms for, he's lost.

As a parent, it's very difficult, as these parents can attest to, to stand by and watch your child get weaker every day, and you feel totally and completely helpless. You never feel like you're doing enough to get your child better.

I've been constantly checking clinicaltrials.gov, trying to find some sort of trial that Joshua could be part of. But unfortunately because he's 14, unfortunately because he lost the ability to walk a long time ago, most of these clinical trials don't want him.

We thought in March of this year that we

were in. We went to Johns Hopkins, and we applied for one of the exon 51 skipping therapies there. We spent the entire day at the hospital, went through all the hoops, and then found out that because he couldn't lift a glass of water to his mouth -- he had lost that ability -- he could not be in the study. So that was heartbreaking for Joshua to lose that opportunity to take one of these therapies that are available.

When asking Joshua what he would like me to say today, we're not asking for miracles. We're not asking for him to jump out of that chair and run around the room. But he would love the ability to gain his arm strength back.

He would love the ability to feed himself at lunch and not have to go eat in a separate room at high school apart from everybody else because he has to have an aide feeding him. He would love to be able to throw a ball and play hockey with his brother. He really would love the opportunity to just gain a little bit of that control back.

Joshua sets high goals and he's a high

achiever in a lot of areas. In academics, he's an absolutely brilliant mind trapped in a body that doesn't work. He's achieved a perfect store on his standards of learning. He's in the gifted program. He's SPL of his Boy Scout troop. He's vice president of student council.

But unfortunately, with Duchenne, he's also a high achiever. He seems to be progressing at a higher rate than a lot of his peers. So now more than ever, time is of the essence for our family to get some sort of therapy other than steroids, which is clearly not doing anything for him.

Despite this physical decline, he's very motivated, very positive. He wants an advanced studies diploma from high school. He wants to go to JMU, and he wants to be an FBI intelligence analyst. So we'd ask for the opportunity to approve drugs like this to prolong his life enough that he can meet these goals. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 16 step to the podium and introduce yourself? Please state your name and

any organization you are representing for the record.

MS. McSHERRY: Hi. My name is Christine McSherry, and for disclosure, I run an organization, Jett Foundation. Jett Foundation has received educational programming from the sponsor.

I am the founder of Jett Foundation, a Duchenne nonprofit started 16 years ago when my now-20-year-old son Jett was diagnosed with Duchenne. I'm here to tell you my story, my family's experience with drisapersen, and why it was not an option for Jett.

He, like others but not all, experienced side effects, which you've heard about today from both the company and the agency. When Jett was diagnosed in 2001, there were no options. Duchenne was terminal, and there were no drugs in the pipeline.

When I heard of Prosensa's safety and efficacy trial, we agreed to participate. The year was 2010 and the site was 17 hours by car from our home in Boston. We drove those 17 hours three

times between Thanksgiving and Christmas, leaving four other young children at home.

During a two-week stay, Jett received three doses over three days, subcutaneous injection into his belly. By the third injection, we knew he was getting drug, as the sites were inflamed and incredibly painful. Even if this was an effective treatment, there was no way Jett could tolerate it, and he said so himself. It was a very long drive home.

Christmas approached and he could no longer walk on his own. And while we waited for words of a promised extension study, it never came. And we knew that even if it did, the risks would not be manageable for Jett.

For Jett, what did an injection site reaction actually mean? It meant it was extremely painful when the drug was injected. It meant that the sites immediately turned red and swelled. They stayed that way for months, and then they turned purple.

It meant interference with his bathing, his

dressing, his transferring, his sleeping, and worst of all, in the summertime, the embarrassment of the purple spots on his belly. Still today, five years later, he has three large hardened welts on his stomach.

Had Jett remained on drug, by my own estimate, he would have 250 of these injection sites. There is no way that Jett could manage those risks. And in the context of all that you've heard today, all these safety risks that we've discussed, these are the least severe.

So as you deliberate, please remember, the risk to patients like Jett is not manageable. For patients like Jett who are exon 51-amenable, we need other options. And for those patients in our community who are not exon 51-amenable, the unmet need remains, and it's significant. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker number 17 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. DENGER: I have slides.

DR. BAUTISTA: Could you please state your name in the record, first?

MR. DENGER: Oh, I'm sorry. Brian Denger. My name is Brian Denger, and I live in southern Maine. And my travel was also provided by CureDuchenne and the EveryLife Foundation.

My sons were diagnosed in 1997. My family's story is much like the others affected by Duchenne, both in what we've experienced and the window of what is to come. My sons were healthy infants, yet their physical development lagged their peers as toddlers.

My wife and I became concerned with their frequent falls and difficulty climbing stairs. There was no family history of muscle disease. The diagnosis ultimately came out of the blue, and the disorder advanced differently for my sons.

Progression and weakness came quickly for Matthew, and he soon became dependent on us for all of his physical needs. Despite his condition, Matthew attended college full-time. Yet he died

two months prior to his 21st birthday from cardiomyopathy, after spending a full day in classes.

Patrick rode a bicycle and walked until 13. He is in his third year of college. He drives an adapted van using hand controls, giving him much independence. I hope he is able to do this for a long time.

So we need the wisdom of Solomon, yet time doesn't allow us the patience of Job. The window of opportunity here is too brief, but it shouldn't prevent us from being mindful. There will be risks for patients should drisapersen be approved.

My sons were prescribed steroids to preserve strength and function. We discussed this frequently with their doctors, making our decisions with information and their medical support. Should drisapersen be approved, I will speak with my son and his doctors, and together we will decide whether taking the drug is right for him.

Ultimately, each person is an N of 1. Recognizing that there is a spectrum of progression

in individuals with this disorder highlights the need for a number of therapies. Drisapersen could be one of those options.

The more options that become available, the better the chances are that people will find a protocol that is right for them. I've lost one son. Little that I have experienced has been more difficult. That's a significant side effect that all of us affected by this disorder live with.

If the data shows efficacy in drisapersen and it is approved, I will speak with Patrick about this drug and we will seriously consider the risks. Like you, I will scrutinize the data carefully. I have agonized over this for some time, considering these data in our experiences.

It is my belief that approval of this drug for a broader cross-section of patients with long-term postmarketing safety studies will serve this community well.

Patrick's health is still very good and he is not chasing his dreams, he's working on his plans. Having new therapies to help him to stay on

that course would be wonderful. I hope that the data shows drisapersen can be one of those options. Thank you very much.

DR. ALEXANDER: Thank you.

Is speaker 18 available to participate? Speaker 18?

(No response.)

DR. ALEXANDER: We understand that speaker 19 is not available, so we'll move to speaker 20. Will speaker 20 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. HERMAN: Good afternoon. My name is Mary Herman. My travel and lodging here were provided by CureDuchenne and EveryLife Foundation.

I am the parent of a boy with Duchenne muscular dystrophy. I am also a practicing family medicine physician. I look at drisapersen both as a parent and as a doctor. Our son Jacob was diagnosed with Duchenne at age 2 and a half. Having the words "progressive," "degenerative," and "fatal" applied to your child is a horrific

experience.

Jacob entered the U.S. trials of drisapersen in 2012. He was 10 and a half years old, unable to keep up with the other boys as they peeled off into sports, unable to run with anything more than a trot or even to jump with two feet off the ground.

Jake finished the 28-week trial and later 3 months extension treatment, and then was off drug for 14 months. He's been back on drug for the last 12. After unblinding, we found that Jake had been on the highest dose. We were not surprised as he had clearly improved in strength and endurance.

Concurrently with the drisapersen study, Jacob participated in a UCLA study of the natural history of Duchenne. Every 6 months, his strength and function were extensively tested.

After the awful phone call from Dr. McDonald in September of 2013 telling us that the trial had been suspended, I asked the UCLA researchers to pull out Jacob's data, and that data confirmed our impression that the drug was working.

The data from the UCLA and drisapersen

trials and our observation of Jacob's improved function in daily life convinced us of the life-changing value of this medication. Aside from some manageable injection site reactions, Jacob has had no significant side effects.

During the UCLA study, every 6 months I filled out the same questionnaire. One of the questions was, "How satisfied would you be if your child could stay at his current functional level?" And I would always think to myself, where is the choice for "ecstatic"?

I would be ecstatic if Jacob could stay at his current functional level, if we could kick the words "progressive" and "degenerative" and "fatal" to the curb. And I feel that that is what drisapersen has allowed us to do.

At age 14, our son is still ambulatory and attends school without an assistive device. He is independent in activities of daily living. He does have trouble climbing stairs now and uses his scooter for long distances.

Much of this decline, however, happened

during the excruciating 14 months when he was off of the drug. His decline slowed and has now stopped since restarting drisapersen, and I have seen this in him and in his individual study data. After observing his rate of decline while off drug, I am convinced that had he not resumed drisapersen, Jake would not be walking today.

Clearly, there are moments when statistical analysis has not yet fully captured the true benefit of a drug. For Duchenne patients, drisapersen and the other AON therapies that are close on its heels represent a huge leap forward into the new possibilities of getting better and of not getting worse.

We urge your approval of this life-changing drug and appreciate your discussion of the overall strengths and weaknesses of the data supporting the efficacy of drisapersen. Thank you.

DR. ALEXANDER: Thank you very much.

Is speaker 21 available to participate in the hearing? Speaker 21?

(No response.)

DR. ALEXANDER: Okay. We'll move on to speaker 22. Will speaker 22 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. ARRAS: Dear committee, my name is Philip Arras. This is our son Maxime. And I represent the Duchenne parent community specifically of the boys taking part of the drisapersen study with Dr. Goemans in Belgium. I came over here by invitation of CureDuchenne, who covered my expenses.

Today I'm speaking to you as a father of a 16-year-old boy with DMD. Our son, Maxime, was born a happy baby. He developed a walk when he was 2 years old, and somehow his walk remained unstable. He constantly stumble over his own feet and he kept falling to the ground.

At the age of 5, he was, after extensive medical testing, diagnosed clearly with Duchenne muscular dystrophy. Having little stamina, his stroller became his best friend, and as he kept losing muscle strength, his future became

uncertain.

At the age of 8, Maxime took part of Prosensa's medical study at the Leuven Hospital in Belgium. Some time after starting the injections, we noticed physical improvement in his behavior, as if he had more energy left at the end of the day.

After a year, Maxime went into the hospital every week to get his injection. As the study continued, the physical improvement became significant. He became stronger. That gave him the ability to walk longer, to walk longer distance, walk easier, and even walking the stairs became possible without using his hands as support. At school, teachers, for instance, spoke spontaneously how Maxime had become able to participate actively during field trips and at gym classes.

Now, over the next four years, Maxime maintained his muscle strength. The main side effects of these subcutaneous injections were the skin discoloration and the hard tissue under the skin at the places where the injections were given.

These areas, however, were not painful, and given the benefit of the drug, it was worth the reactions.

When Maxime was 14 years old, the study was put on hold. After 6 months, he started to feel more tired and he was running short on stamina. We were happy that a year later the study continued with weekly doses of drisapersen through a portacath, which is more comfortable and it avoids skin side effects. After some months starting up again, Maxime was up to the same level of physical strength and ability as a year before.

Today my son is 16 and a half years old. It is so unusual for someone his age with DMD to still be walking and living an independent life as a teenager. He walks daily 350 yards to school, shares in all social activities of his high school. He goes weekly swimming. So to me, it is very clear what drisapersen is capable of.

Our son is a living proof of its positive effect on DMD. I could not imagine our boy without drisapersen because without the drug, it would only

be a matter of time for him to depend on a wheelchair. This is my story. Thank you for your time.

DR. ALEXANDER: Thank you very much.

Will speaker number 23 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. RICO: My name is Tracy Rico. Travel provided by CureDuchenne and EveryLife Foundation.

I am the mother of 10-year-old Tanner Rico, my youngest and only son. When he was just about a year old, the doctor noticed something wasn't quite right with Tanner's health and ordered a slew of tests to be done. When he was 18 months old, we got the heartbreaking, devastating news that Tanner was diagnosed with Duchenne's.

As you can imagine, we were devastated. Everything we had heard and read about Duchenne's was a death sentence. We were told there was advancements in medicine and it was just a matter of time before there would be a cure or even a

band-aid.

During the next 5 years after receiving the devastating diagnosis, our family anguished over the fact that our son would never had the opportunities that his peers have: to surf, to play on the football team, to grow up and be a fireman or a policeman like his uncle.

In kindergarten, Tanner noticed he was different than his peers. Tanner continued to weaken. His hands were cramping when he colored. He struggled to dress himself, climb stairs, but we continued to pray for hope.

Then the day came. Tanner was accepted into a clinical trial. We were aware of the risks and the uncertainties involved. However, the possible benefits outweighed the opportunity of having a drug that would provide a better quality of life for my boy.

On the drug, Tanner started coloring without complaining of his hands hurting, he started brushing his own teeth, he started dressing himself, and he even walked up stairs. These are

accomplishments that we were ecstatic about. And then the drug stopped. He started losing those abilities that he had once gained after about 3 months of not being on the drug.

Tanner is back on drug, and he's starting to regain stamina again. We're asking for you to please approve this drug as time is not a luxury, and Tanner has dreams and ambitions of growing up and being a daddy and a father just like his own. Thank you.

DR. ALEXANDER: Thank you very much.

Will speaker 24 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. MILLER: Hello. My name is Debra Miller. I'm the CEO and founder of CureDuchenne and the mother of a son with Duchenne. CureDuchenne provided funding for drisapersen and for Sarepta Therapeutics' exon skipping drug etaplirsen.

The families you've seen here today have seen and experienced the effects of drisapersen,

consistent improvement in every boy here with drisapersen. They've all experienced relentless decline when they were off the therapy, and when back on therapy, all the boys gained back at least some of the function lost during the interruption even though they were much older. They've waited patiently to allow the FDA system to work for them.

Doug Penner can walk 6 kilometers. Sixteen and a half year old Maxime walks almost a quarter mile to school with a backpack and home again. Gavin plays soccer and runs across the living room, leaping onto his couch. Absolutely no 10-year-old boy with Duchenne can do that. This is a result of drisapersen. Nicholas can go from the floor to the couch. This kind of independence in life-changing.

Fifteen-year-old Simon started riding a bike. McKenzie broke his leg. How many other 15-year-old boys with Duchenne can walk again after a broken leg? Brody's pulmonary function tests were so improved that his physician repeated the tests. He went from falling three times a day to not falling in over 2 months.

Our community is encouraged we are at an advisory committee, and I'd like to challenge ourselves to look at things from the patient perspective. I've heard so much about FDA's enlightened flexibility for rare diseases and the importance of bringing together data and integrative thinking when a true unmet medical need exists. Today we encourage both the panel and the FDA to be enlightened, strategic, and to consider the benefit to the patients of the drug that's been discussed today.

I wish we were talking about a potential cure, but I accept great progress occurs in steps. Drisapersen approval would represent a great first step and can be done in the hearing now.

As a mom who knows the devastating course of Duchenne, I've seen the benefits of drisapersen. Drisapersen extends ambulation and independence and improves quality of life.

Many parties here have responsibility: the FDA to allow access to this drug without delay; the sponsor to assure safe and appropriate use in a

commercial setting and to continue to answer the unanswered questions. Advocacy organizations have to share expectations that are realistic, supportive further research, and partnering to build knowledge.

We know what the side effect with Duchenne is, premature death. We have two options. You can support approval of drisapersen. You can take an important first step of making a difference to prolong ambulation, sustain independence, and allow these boys to plan for a full life. Or you can leave this community to do what we have always done, prepare for their wheelchairs and lose our sons before the age 30.

I have realistic hope that you'll find the right lens through which to review this data. Our boys are counting on you. Thank you.

DR. ALEXANDER: Thank you very much.

Next, will speaker number 25 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MAXIME ARRAS: Dear Committee, my name is Maxime Arras and I represent the patients with Duchenne illness that takes part of the drisapersen medical study, including my friends here. I came over to the U.S. by invitation of CureDuchenne, who covered my expenses.

(Video played.)

MR. MAXIME ARRAS: Thank you for watching my video. You are probably surprised to see a 16-year-old boy with Duchenne that walks and jumps and steps in the stairs. Well, in my case it's all thanks to drisapersen.

I still remember that when I was 7 years old, it took me great effort to walk a longer distance. I was always getting tired quickly and asking to sit in the stroller or on my dad's back.

That all changed 7 years ago. I took part in the drisapersen study at the Hospital of Leuven in Belgium. Every week I went to the hospital to get an injection of this drug. It was amazing that some time after getting the injections, I could feel that I have more energy left in my legs and

arms.

Half a year later, I was able to walk longer distance without getting tired. At school I could participate in more active games with my friends. And I even got the strength to learn how to swim and ride a bike.

Today I live an active, independent life. It takes me 10 minutes to walk to school. At school, I'm able to change floors by stairs after every class. For longer field trips, I take my walking scooter. I also often use public transportations to go to the movies with my friends.

I'm so grateful that I get drisapersen because it keeps me walking. My heart hurts for all the other Duchenne boys I meet who don't have access to this drug. Some of them are younger than I and are already in a wheelchair. I wish that every boy soon will get access to drisapersen because I know and I feel that it works.

Thank you for listening, and please don't take this drug away from us.

(Applause.)

DR. ALEXANDER: Thank you very much.

Will speaker number 26 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. CRAWFORD: Todd Crawford, and this is my son McKenzie. Our travel was provided by CureDuchenne and the EveryLife Foundation.

The lives of our children have milestones. We know their birth date, the day they started kindergarten, when they turn double digits and sweet 16, followed by high school and college graduation, marriage, and then the birth of their own children.

McKenzie was diagnosed with Duchenne muscular dystrophy at age 4, so he traded a lot of the typical childhood milestones for some of the less typical. Little League baseball lasted only 3 years because he didn't have the strength to swing a bat. Running was replaced with trying to walk just far enough to avoid the need for a

scooter.

There are heart-wrenching milestones, like losing his ability to climb stairs, walk long distance, or get himself ready for school. Eventually he will lose the ability to raise his arms and hug us goodnight.

In 2011, McKenzie was enrolled in the drisapersen trial. We were excited to be part of the study even though he was first placed in the placebo-controlled group. During this time his strength declined to the point where he could no longer complete the same tasks that were originally required to qualify for the clinical trial. Fortunately, McKenzie began receiving full doses of drisapersen during the open label phase.

Two months ago, shortly after completing his 49th weekly injection, I was sitting in a hotel room 2,000 miles from home when my wife called to tell me McKenzie fell, and she was certain he broke his left leg. Yet another milestone in a child's life, but one we dreaded.

She was correct. He had comminuted

fractures in both his tibia and fibula. I immediately made arrangements to fly back home, and I sat in the room and cried. Why did I cry over such a typical family milestone? Very simply. Because I've read enough about this scenario time and time again with teenage boys who have Duchenne muscular dystrophy. They are atypical in regards to regaining their ability to walk.

Surgery was ruled out, and ultimately we decided to only cast his left leg. However, we elected to cut the cast off four days later to avoid muscle atrophy. The good news is that McKenzie was standing 3 weeks after his fall. He started rehab 4 weeks post-break. He walked 15 minutes on an anti-gravity treadmill in week 5, and by week 7 he walked unassisted for more than 400 feet.

For a boy with Duchenne, there is nothing normal about his broken leg or his recovery. It is my most sincere belief that drisapersen preserved his muscle and allowed him to avoid the effects of muscle atrophy and to maintain his ability to walk.

McKenzie has experienced the reported injection site reactions. However, we consider those to be table stakes for his participation in a treatment that has preserved his ability to walk at age 15 following a significant leg injury.

I want to leave you with a thought in closing. When our sons break their legs, their only worry should be whether or not they want a red, blue, or camouflage cast, and they should not have to worry about when their wheelchair will arrive.

A cure for this disease cannot happen until we get a first treatment approved. I respectfully request that you grant approval for drisapersen. Thank you.

DR. ALEXANDER: Thank you very much.

I understand that speaker 27 is not here to participate in the hearing, so we'll move to speaker 28. Will speaker number 28 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WOODS: Hi. My name is Charaine Woods. This is my son Damon Woods and my father Charles Reynolds, and our travel was provided by CureDuchenne and EveryLife Foundation.

As soon as my son was diagnosed, my immediate response was, "Is there a cure?" I felt a sense of impending doom. The walls closed in on me as the doctors told me there is no cure.

When Damon was accepted into the study, a weight was lifted. I quit my job so that my son could have a chance at a normal life. Taking him back and forth to the study site was a pleasure for the both of us, even with the uncomfortable injection sites. As a mother, I finally felt useful. I was finally able to take some control over this horrendous disease. I no longer felt helpless.

Without this drug, I wouldn't have had the opportunity to watch my son play long childhood games, simple things that children of healthy parents take for granted. This treatment has given my son and my family hope, strength, and endurance.

Our first trip to the physical therapist after Damon started in the study was invigorating. She was shocked and confused by his increase in strength. When the study stopped, our physical therapist confirmed that Damon was declining. Unfortunately, during the time that the study stopped, my son sprained his toe and has never regained ambulation.

However, this drug means more than just being able to walk. For my son and many others, this drug is a gateway to a quality of life for them, even in a wheelchair. I'm pleading with you, please give our sons a quality of life.

Time is not on our side. Our children need this drug now. Our children have plans for their futures, just like yours. Damon wants to go to medical school and cure cancer. The difference is, as a parent with a child with Duchenne's, we are consumed, distraught, and overwhelmed about our children's lives, literally.

Thank you for all your time and all your hard work. We appreciate it.

MR. REYNOLDS: Hi. My name is Charles Reynolds. I'm Damon's grandfather.

I never had a son, but when I found out my daughter was having a son, I was overjoyed. I said, yes, this is my opportunity to share my life with him. I was a basketball coach. I was a football player in high school and college. So I was going to put everything I had into Damon to actually help him.

You know, seeing Damon and noticing that he wasn't able to walk any more really made it difficult. It broke my heart into a million pieces. I couldn't bear the thought of actually seeing him this way. And as you as a grandparent, as you as a parent yourself, if you have a son like that or a grandson like that, you probably couldn't bear the thought of that, either.

But here we are at this critical point, this critical junction in life. But we all need to make a tough, tough decision. Please, please make a decision and help my grandson, to help my son, which is Damon. Thank you.

DR. ALEXANDER: Thank you very much.

I understand that speaker 29 is not here to participate in the open public hearing, so we'll move to speaker 30. Will speaker 30 step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. LOPEZ: My name is Roger Lopez. I'm here representing the International Association of Fire Fighters. My travel was provided by the International Fire Fighters Association.

Thank you for your time and the opportunity to speak with you today. The IAFF is nonprofit service labor organization representing over 300,000 firefighters and emergency medical service providers in the United States and Canada. Our members serve cities, towns, and fire districts in every state and territory.

The IAFF is based in Washington, D.C., with a national network of over 3,000 local affiliates. For over 60 years the IAFF has stood shoulder to shoulder with the Muscular Dystrophy Association in

on the ongoing fight against the more than 40 neuromuscular diseases that are claiming the lives of children and our fellow firefighters.

Through our Fill the Boot Campaign and various other fundraising events, we have helped MDA fund the research that is now resulting to the development of breakthrough therapies for these devastating diseases. To date, we are proud to have contributed over half a billion dollars of funds to help find an end to diseases like Duchenne's muscular dystrophy. Our commitment to this fight is unwavering.

This year alone, more than 162,000 of our firefighters volunteered their time at more than 3,000 events across the country to raise money to help support this mission. But our hard work and deduction go beyond our commitment to fill the boot. We are in this at a personal level.

Every year, many of our firefighters around the country dedicate a week of their time to volunteer at MDA summer camps around the country. These are places where kids can go and get a

traditional summer camp experience despite the challenges that they face living with their disease.

Last summer, many of our firefighters had a chance to share a week with these amazing children at camp. I myself have participated every year for the past 13 years. I look forward to it every summer. It is truly a life-changing experience.

We are also committed to this effort on behalf of our many firefighters who are directly impacted by those diseases because they or their children or loved ones have been diagnosed with a neuromuscular disorder. We want to see safe and effective options for everyone with Duchenne's and the other related diseases.

I am not here today as an expert on the science, so it is not my role to suggest what the outcome should be. But we as firefighters want to take this opportunity to express our support for finding therapies that could improve the lives of people that we love and support, people living with muscular dystrophy.

We have led this fight for more than a half a century, and we are proud of the IAFF's many contributions. And we will continue to fight alongside the MDA to fulfill the promise from the earliest days of our partnership, to join forces and fight back until cures are found.

Once again, thank you for your time, and thank you for this opportunity.

DR. ALEXANDER: Thank you very much. And our 31st and final speaker, if speaker 31 could step to the podium and introduce yourself. Please state your name and any organization you are representing for the record.

MS. CATE: Hello. My name is Tammy Cate, and this is my son Seth, who is 9. Our travel was provided by CureDuchenne and the EveryLife Foundation.

Seth loves baseball. You can see the determination on his face. Though it's not easy for him, he is determined to do the things he loves, and I'm determined to do what I can to help him do them longer.

Over 3 years ago, we began a long journey on a clinical trial drug. At the start of that trial our son was 7 and doing the things that most 7-year-olds do. We thought we saw a drastic improvement such as running, jumping, and playing baseball. However, later we found out he was on placebo.

Following the trial we began receiving the actual drug. We noticed the injections were more painful, but were hopeful now on drug we would notice differences. This is Seth consoling his service animal following an injection. As he said, "It's worth it. It's okay. It doesn't hurt too bad."

While on drug, we noticed his energy level increase, as did his teachers. They commented on his abilities during recess. A few months later, the drisapersen study was halted. We were devastated. During this time we did notice declines in his energy and walking ability. Seth was concerned about not having the medicine to help himself and other boys.

About a year ago, Seth began the drug again. We were excited though anxious. We did not want to experience another letdown of lack for statistical significance again. However, he agreed to the study because he desperately wanted a cure, and so did we.

Since redosing in 2014, we were concerned because we did not see major improvements. However, his doctors and PTs had another story. The PT was impressed by his strength and abilities. She showed us in research and in practice how most boys his age with DMD were on a rapid decline and were no longer walking. She was impressed that he was actually improving and remaining stable.

He does have injection site reactions all over his body. These are difficult to look at but not painful. This and other risks are minimal compared to the risk of DMD. Just last week, he was showing off his jumping ability and stating the drug must be working. We look forward to this and other drugs coming down the line for everyone with DMD.

At a recent coach to cure D [indiscernible] event this fall, Seth was lifted up by some college players. You can see the joy in his face. Later he asked, "Mommy, when they find a cure for DMD, can I play football?" To which I replied, "Maybe."

We know it's not just about playing a sport but living a life. We are in a race against time for a cure for us and the families coming behind us. We do want to win this race. Thank you for your time and assistance with helping us make this a reality.

Clarifying Questions (continued)

DR. ALEXANDER: Thank you very much.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. 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 have about 20 minutes for continued questions for the sponsor and the FDA before we turn to the formal questions at hand. So I'd like

to begin by offering the sponsor an opportunity, if there were items from before lunch that you wanted to address, remaining questions that had remained open.

DR. MCDONALD: Prior to lunch, Mr. Cassidy had asked the question about the CINRG natural history study data.

As study chair of the CINRG Duchenne natural history data, I can report that we haven't just been working with one sponsor to provide the natural history data. We've actually actively been working with multiple sponsors over the past year to provide natural history data to help with study design for other therapeutics and also help with efficacy analysis.

We're currently putting together a consortium of sponsors to make the data available to multiple companies and also extend this important natural history data. BioMarin was actually the first to commit to participate in this consortium, and others have joined in as well, and we're excited about what this will inform us with

regard to long-term effects of the treatment.

DR. ALEXANDER: Thank you very much.

We'll move directly to questions.

Dr. Bagiella?

DR. BAGIELLA: I had a question. There was a discussion about the cut points in terms of the 6-minute walk. So what was your rationale for choosing the 330 meters as a significant or meaningful cut point?

DR. FUCHS: The rationale was based on literature, publications of prognostic factors. And I think one of the great things that we've learned as we've gone back and forth with the agency -- it was referenced in the open public session earlier -- is that it's hypothesis-generating.

Now, the larger picture for us in this regard is that it's not a surprise that there is variability in the outcome as you move definitions of the population around. There are probably complex predictive factors that play here.

Fortunately, we have two other randomized

trials to put one trial in the context of, and we can corroborate that we observe similar benefits and similar populations in the clinical trials.

I think, as I've said during the core presentation, it was not our intention to turn a subgroup hypothesis-generating exercise into something that's stand-alone, but rather simply to corroborate that the findings of the earlier studies were in fact confirmable. Thank you.

DR. ALEXANDER: Thank you.

Dr. Zivin?

DR. ZIVIN: For the sponsor, I'd like to know two questions. One is, what was the dose-limiting side effect that caused you to pick the dose you did?

DR. FUCHS: I believe, and Dr. Campion --

DR. ALEXANDER: Can you ask your second question at the same time in case they can address both?

DR. ZIVIN: Okay. The other one is simpler, I hope. How far can a normal boy walk in 6 minutes as opposed to your typical Duchenne dystrophy 7-

year-old?

DR. ALEXANDER: Thank you. So the first question was what the dose-limiting side effect was, and the second was how far can a normal boy walk in 6 minutes.

DR. FUCHS: Pyrexia at higher doses in that regimen and route of delivery, and normal 6-minute walk distance for this age range of boys is around 600 meters.

DR. ZIVIN: And how much were the 7-year-olds in your group walking?

DR. FUCHS: Sorry. I didn't understand the question?

DR. ZIVIN: The Duchenne patients, how far can the average 7-year-old walk?

DR. FUCHS: It's dependent on other factors, but I think at our trial, the average 7-year-old in study 1 and study 2 did about 400-or-so meters. So about two-thirds of predicted.

DR. ALEXANDER: Thank you.

Dr. Green?

DR. GREEN: We've been focusing a lot on

skeletal muscle. But when I hear the public comments, a large amount of it has to do with energy level, not just weakness. And when I look at the protocol, it looks like in terms of cardiac status, there was an EKG done. That's about it.

Has there been any work in terms of this agent, perhaps its mechanism, on echocardiograms, cardiac output, pulmonary functions?

DR. FUCHS: We have done some work on pulmonary function in the ambulatory population. Their baseline percent predicteds in the ambulatory population are in a fairly close to normal range.

Part of the reason that we believe that pulmonary function improvements are not detected as secondary exploratory endpoints in the trial is because they're closer to normal. You have to move substantially to a more advanced population to investigate pulmonary functional improvements.

As far as cardiac findings, we find no adverse cardiac findings from a safety perspective. We reviewed those fairly carefully. And again, you'd have to study an even further progressed

patient population. And I think the impression to get about Duchenne, as I listen, a very heterogeneous disease.

As the disease progresses through stages, it can be very difficult to capture in a single primary prospective endpoint, a single measure of benefit of treatment. And the impression that we get from reviewing the data in the ambulatory population is how consistent the findings are.

They move around a little bit, no doubt. But on the other hand, the consistency of the benefit trial to trial in comparable populations remains the main finding.

DR. ALEXANDER: Thank you.

Dr. Mielke?

DR. ONYIKE: Yes.

DR. MIELKE: Yes.

DR. ALEXANDER: I'm sorry. The question was for Dr. Mielke over here.

DR. ONYIKE: Oh, sorry.

DR. MIELKE: Sorry. Two hopefully relatively quick questions.

Before we took lunch, we were talking about the injection site reactions, and you had shown that there really was no difference in terms of efficacy as to whether people reported whether they had a reaction or not.

But it sounds like when people do have reactions, particularly on the drug, that they're quite severe in some cases. And so I was just wondering if you had looked at the severity of the reactions as a potential way of unblinding as well.

DR. FUCHS: Let me start by saying I think the reactions that progress, progress after about 48 weeks, and the blinded trials were principally 48 weeks and under. And the more severe injection site reactions, things like induration sclerosis, you saw median onset times in the presentation that were substantially later and less frequent at week 49, week 50, et cetera. So we don't think there's a contribution of the more severe reactions.

DR. MIELKE: And one other quick question because heterogeneity keeps coming up a lot. And so from the disease standpoint, in predicting who

may decline the fastest and whatnot, is the walk test the best predictor? Are there other predictors of heterogeneity? Just to figure out who to potentially target a drug to as well.

DR. FUCHS: We've created models of prognosis using what I think is a fairly large natural history data set, our internal placebo-controlled trials. And we can find I think it's three or four prognostic indicators. Age, baseline walk, rise from floor time, and North Star ambulatory assessments are all prognostic indicators.

They're not necessarily predictive indicators, necessarily, and they don't necessarily all flow in the same directions. So that's part of what makes for this complexity. You have the interaction of prognostic indicators in the control arm and then predictive indicators in the treatment versus control arm.

As I said, I think it's those mixes that explain variability from trial to trial. And again, what's most impressive about the results is

when you look in comparable populations. Consistent results for 6-minute walk distance are observed.

I might also add that for all of its limitations we've talked about as a treatment benefit indicator, demonstrating consistent evidence on that type of an endpoint is itself also something that impresses.

DR. ALEXANDER: Thank you. I'd like to ask a question about future studies. You've emphasized that the trials were conducted more or less concurrently, and also identify nearly a dozen factors that I presume are provided as a basis to explain either the somewhat different study designs or the results that may otherwise seem inconsistent.

So you mention ataluren was developed. Regulatory guidance for DMD has been developed. Natural histories have been published, new knowledge regarding heterogeneity, prognostic factors for disease progression, variations in clinical care, clinical relevance regarding

biomarker assessments, and relevance of 6MWD assessments. You also highlight a variety of mechanisms that may account for the findings of a lack of consistent increases in dystrophin.

So my question is this. Other than a loading dose for all patients, if you knew then what you know now, what would be the study design? That is, what are the ways that you would be doing this development program differently and designing a trial with all of the information that you now have?

DR. FUCHS: Probably we'd want to stratify randomization by key prognostic factors within key windows where imbalances in randomization can become relevant. Probably we'd want to restrict eligibility in key clinical trials involving ambulatory functional assessments as a primary outcome variable.

Might like to explore the impact of alternative doses and regimens on outcomes. One of the biggest challenges there, of course, is what's going to be the immediate or readout endpoint. The

program has been informed by clinical outcome variables, which is fantastic. As we move forward, I think we'd have a parallel interest in better understanding what could be measured in a more facile way. Those are just some of the things that come to mind.

As a practical matter, you have heard our colleagues describe the prevalence, for example, of the U.S. ambulatory population. And controlling for numbers of these factors in achieving some of these effects might be very difficult.

If we were to move or broaden the population, we'd be into a project of developing and validating endpoints. And that's also a tremendous undertaking, as the patient population advances in illness vary.

DR. ALEXANDER: Thank you.

Mr. Cassidy?

MR. CASSIDY: One of the most severe and common side effects of the drisapersen is thrombocytopenia. Quoting from the sponsor data, it is "a recognized class effect of anti-sense

oligonucleotides, although the precise mechanism is not well-understood, and additional risk factors of the delayed onset of severe thrombocytopenia absorbed in drisapersen studies have not been identified."

Is there any plan to further investigate how precisely AONs induce thrombocytopenia and why, and why the onset of thrombocytopenia is always so late?

DR. FUCHS: If I could, I'll start with the short answer, and then we can dig in further if you like. We have an expert hematologist here to help us.

There are two different patterns of platelet alterations. The significant one that you're asking about is a late-occurring event. It is accompanied by the presence of antibody to the platelet glycoprotein IIB/IIIA. It reverses on withdrawal of drisapersen. And in preclinical studies, if you rechallenge primates who have experienced severe thrombocytopenia, the severe thrombocytopenia returns.

So our belief is that you need a combination of drisapersen and this particular antibody. Fortunately, you can test for this antibody. It's not an antibody to drisapersen, it's an antibody to the platelet. When you take the drisapersen away, the platelet recovers and patients are back to normal.

Unfortunately, that patient should not go back on drisapersen. But fortunately, that's very rare. We probably have more details, but in the interest of keeping it moving, I'll turn it back to you.

DR. ALEXANDER: Thank you. Yes. There are a number of other questions.

Dr. Foley?

DR. FOLEY: My question is about the concomitant steroid regimens your patients are on. And the second question I have also -- if you could comment on the portacath. One of the patients mentioned he was getting his medication via portacath.

DR. ALEXANDER: What precisely is the

question regarding steroids and portacaths?

DR. FOLEY: From the perspective of a pediatric neuromuscular specialist, it's very interesting to know if your patients are on daily steroids or intermittent.

DR. FUCHS: We created a group of patients based on the data as to whether they were on continuous steroids or intermittent corticosteroids, and we found no substantial difference in effectiveness across the program according to what underlying corticosteroid regimen they were on.

I'm sorry, your second question just flew out of my brain.

DR. FOLEY: The portacath.

DR. FUCHS: We have done a limited amount of development of intravenous delivery of drisapersen. We are a maker of enzyme replacement therapy for three other conditions that are marketed that we're the license holder for, so we have a great deal of appreciation for the challenges of intravenous delivery.

Subcutaneous delivery is really a great option for patients, but it's also not a situation. And I think we heard this from some of the speakers, that one size fits all. So part of our continued interest in development of drisapersen, will we be able to enable options for other patients if the sub-Q injection site reactions are problematic. That program is early. I can provide more data if you're interested..

DR. ALEXANDER: Thank you.

Dr. Onyike?

DR. ONYIKE: Yes. This question is directed to Dr. Wagner, if she's still here, and Dr. McDonald.

I want to understand. I'm trying to reconcile what we've heard in the public comments from some of what we're seeing in the data, particularly the endpoints. What is the normal ebb and flow, if you will, of symptoms, and in particular of these endpoints, in the course of caring for patients in clinics?

DR. FUCHS: We're going to bring both

doctors up.

DR. MCDONALD: I think the endpoints that we're discussing, the time function tests, are routinely done in clinical practice. More recently, the North Star has been added as a Duchenne-specific measure of ambulatory function.

I think what's most striking to me is that in study 1, when we actually have a loading dose and a full 48 weeks of treatment, what we see is really a rather robust treatment effect.

We see a 2.9-second improvement relative to placebo in time to rise; a 4.9-point improvement in the linearized North Star, which has been the more recent way to handle the North Star data, has been a 100-point linearized method, and we see a 4.9-point improvement in the North Star; and then in the Peds QL neuromuscular model, a 7.9-point improvement relative to placebo, and in the generic Peds QL, a 7-point improvement relative to placebo.

These are very robust treatment effects. So I think the stories that you're hearing here anecdotally are not surprising to me because of the

need for a loading dose and also the duration of time it takes to reach peak tissue concentrations.

DR. FUCHS: And Dr. Wagner, did you want to --

DR. ONYIKE: If I may just clarify. What I'm trying to understand is how a person might see an improvement after a clinic visit. So from visit to visit, really, and at the individual level, is there an ebb and flow in clinical measures? What's really what I'm after.

DR. ALEXANDER: Thank you. And if you could announce your name as well prior to responding.

DR. WAGNER: Sure. My name is Dr. Kathryn Wagner. I'm a neurologist at Kennedy Krieger and the Johns Hopkins School of Medicine. I've been treating boys and young men with Duchenne for greater than 15 years. I'm compensated for my time today, but I have no financial interest in the outcome of the proceedings.

So if I'm understanding your question, does an individual get better and worse over time? And after the age of approximately 8, certainly by the

age of 10, no. We see relentless progressive decline. It is extremely unusual for people to get better.

It's extremely unusual for patients to get better in their teenage years. It's extremely unusual for a patient to be stable. Perhaps we might see that over 6 months. It's very unusual for us to see it over 12 months. So for patients, for instance, to be stable in their teenage years for years is not the natural history of this disease.

Am I able to address a previous question?

DR. ALEXANDER: Briefly, sure. Thank you.

DR. WAGNER: Your colleague next to you asked about the fatigue that many of the patients were experience, I just wanted to explain that improvements in skeletal muscle function can also lead to reduction in fatigue because you have better economy of gait. When you improve your skeletal muscle, regardless of whether it affects your cardiopulmonary, you do improve fatigue.

DR. ALEXANDER: Thank you very much.

Dr. Farkas?

DR. FARKAS: Thanks. First, I just want to take one second, if I can. It's always so difficult. There's this silence from the FDA after everybody speaks, and I think we're very grateful that you came and you spoke to us, and that we're listening to you. And I don't think I can have time to say more than that before I move on.

But the question about the clinical course, this is really a profoundly important question because if the disease only gets worse and if we see patients who get better, that would be strong evidence that we can just look at how individual patients are doing and see if the drug is working or not.

But I think we have evidence from the placebo arm of the trials here, and so we were answering in the abstract before. But the data we have are on, for example, Dr. Tandon's slide 30 and 31.

So I think that the answer is complicated. That's what we think. If you take a look at

certain patients with certain characteristics, we have observed that they improve really remarkably over that year. And then if you could show the next slide where we show -- this is a little bit harder to see, but the critical thing is that patients, even in their teenage years, don't only get worse. That's what everybody really needs to understand. And that's why this is difficult to figure out if a drug is working.

There's a patient underneath, from 11 to 12 years old, who's underneath the red or the blue, if I'm getting it right there, who's increasing. And there's other patients through 9 years old. And there's patients who decrease at a visit and then increase again.

So we think that that's the variability over time and the variability over patients' ages that makes things complicated. And we could go through even to slide 32, or maybe even -- if we could take a look at that first, too. We're not saying that this data is showing that patients always get better or that it's easy to figure out. But

patients do go up and down, even at 11 and 12.

Could you also show slide 33?

So with rise time greater than 15 seconds -- I think this is addressing Dr. Mielke's question about variability. So a patient who's a little over 15 years old from one visit to the next can experience, reading off the slide there, something like a 50- or 75-meter increase in 6-minute walk test. So that's the variability that we can actually show, that we know about.

DR. ALEXANDER: Thank you very much.

Dr. Kesselheim?

DR. KESSELHEIM: Thank you. I had a question about whether there was any evidence or intent, if this drug is approved, in having in the label additional instructions on the proper functional parameters or age parameters in which the drug is optimally intended to produce any efficacy and/or additional loading doses if a couple weeks have to be missed because of proteinuria or stopping rules if the functional status gets poor enough that we don't expect

additional evidence of that.

Are there any considerations of those sorts of issues in fashioning a label?

DR. ALEXANDER: Yes, please, if the sponsor could respond.

DR. FUCHS: Yes. Well, first of all, I think what we've submitted in the label, we submit with a little bit of humility around extrapolation of data, acknowledging on the one hand our strongest evidence is in the ambulatory population.

We've requested a broad label in regard to indication, really driven by three considerations. One is supportive data, two is regulatory practice, and three is patient and caregiver preference. And I think a lot of that I'll just quickly whip through; you've heard already.

We do have some data that we believe can form a basis for extrapolation. I think you've heard the agency issued a set of guidelines that pertain to broad label. And third, I think you've heard today patient and caregiver preference. And I'm sure the agency and we look forward to

hammering out the details of that when that time comes. And suffice to say don't want to get too far ahead of ourselves.

As regards stopping criteria, for example, we would say for sure you have to stop if you develop severe thrombocytopenia or an antiplatelet antibody. You must stop if you develop a severe renal injury. Fortunately, those things are both rare.

I would also imagine that the product's label would include the literal results of the trials, all three of them, so that prescribers can make their own decisions about the data so that adequate information is provided. But beyond that, I'd maybe turn to the agency and ask if they have any thoughts about labeling.

DR. DUNN: Yes. I think that right now the labeling question is best addressed by the sponsor. Any labeling negotiations that we're engaged in with the sponsor are not available for discussion here in this forum.

DR. ALEXANDER: Thank you. We just have a

few questions before we'll go to the formal question period.

Dr. Zivin?

DR. ZIVIN: I have two questions that I'd like to have both the sponsor and the FDA discuss. One is, what do you believe is the potency ratio for the primary endpoint?

DR. ALEXANDER: Can you just ask your second one also so we can get a twofer?

DR. ZIVIN: Okay. How do you exploration the discrepancies between yourselves and the FDA on efficacy?

(Laughter.)

DR. ALEXANDER: For two minutes or less.

DR. FUCHS: Well, I'll do the second one first. I think, as Dr. Farkas said, it's a complex data set. And one of the beautiful things about review is the opportunity for scientists to exchange views.

I think where we've landed is that the issues of different mixes of prognostic populations and predictive populations in the studies in part

or to some extent explains the differences in the outcomes of the trial.

Our view is a very much holistic view. As a rare disease company, we've had to make every use of data available that we can. And it's our view from a holistic perspective -- I'll let the agency speak to their view -- I'm not familiar with the term "potency ratio," so maybe while they're developing their answer I can come back to that.

DR. ALEXANDER: Dr. Farkas?

DR. FARKAS: I think that we're going to go around the room and discuss a little bit more one of the questions about our interpretation. I think that's with study 2, as we've called it, about the interpretation of the difference between the 3 milligram per kilogram dose and the 6 milligram per kilogram dose. So maybe when we move to the questions, we'll hear more.

DR. ALEXANDER: Thank you.

Do you want to speak to the potency ratio?

DR. FUCHS: It's a term I'm not familiar with. I have to apologize.

DR. ZIVIN: You're dividing the primary endpoint of the treated group by the control group.

DR. ALEXANDER: If you want to come back to that, you can. That would be fine.

DR. FUCHS: Yes. Thank you. Sorry.

DR. ALEXANDER: Dr. Gunvalson? Ms. Gunvalson?

MS. GUNVALSON: I have a follow-up question that Dr. Alexander made about in hindsight trial design that was answered. And I believe the answer that was given was, in hindsight, there would be more stratification. And that to me means probably a younger, narrower clinical trial cohort.

So I think there's valuable information we can get from the older boys in these clinical trials. All these boys are going to get older. So as we narrow it, I hate to lose the opportunity for the older boys to participate, at least for safety data. So I was just wondering if he had any ideas on that.

DR. FUCHS: That is a question that's a little bit complicated. We see the effect of

the -- my view on study 3 is the broad eligibility criteria were extremely well-motivated, yet we see what happens when you enable broad eligibility criteria. And we create these questions for ourselves about post hoc analyses, about subgroup analyses, and it's very difficult.

If we could instead have unique endpoints for unique segments, that would be fantastic. It's very difficult to do that. The 6-minute walk distance has been the basis of approval by the agency of like 12 different drugs, three of ours. We know it really well.

I don't know that we have as much confidence in the types of endpoints that are needed for what's next and what's next. And we probably have to undertake a fair amount of endpoint development work in collaboration with the agency.

I think it's good that we have a broad eligibility trial, but it does pose challenges of interpretation.

DR. ALEXANDER: Dr. Farkas?

DR. FARKAS: I think that the FDA wants to

reassure the community that we fully support trials enrolling patients across the spectrum of severity. The issue of endpoints has come up a couple of times, and we understand fully that there's not going to be a great deal of knowledge about how these endpoints perform before these studies are done.

We really encourage sponsors to use the endpoints that have been developed, like the pull endpoint in older boys. We think we know enough about that so that we can design trials that would show benefit if it was present.

MS. GUNVALSON: So are you willing to look at just a safety arm in some of these possibly new biomarkers that haven't been proven yet in the older population?

DR. FARKAS: Well, I don't want to go too far away from the most immediate subject at hand. But we think there's a lot of valuable information to be had from boys of drug age, and we think there's a lot of valuable information to be had about biomarkers, too.

DR. ALEXANDER: Dr. Kesselheim, a brief comment, and then we'll move on to the questions.

DR. KESSELHEIM: One of the speakers brought up the expanded access program. I just wanted to hear for a second about what BioMarin's expanded access program for the drug is.

DR. FUCHS: Our history is to introduce expanded access. As we approach the registration decision, we try to make treatment available as early as we can. But we are a little bit reluctant to launch into expanded access if that is in competition with the need for future trials.

One of the considerations and deliberations of the review will be, are there remaining issues that need to be addressed by subsequent, for example, post-approval, trials, confirmatory trials, or additional registration-enabling trials?

Until the review is essentially more fully mature, it behooves us to keep the populations available for clinical trials as opposed to simply open access. That's been our practice.

Through that practice, we have made

medications like Vimizim, our most recently approved medication, available prior to full action once it's pretty clear that we're in the approval pathway, once we and the agency have determined that, on balance, benefit outweighs risk.

Questions to the Committee and Discussion

DR. ALEXANDER: Thank you very much.

We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except for at the request of the panel.

Can we have our first question? So question number 1 is as follows.

Discuss the strength of efficacy evidence provided by study 1 with particular consideration of the following issues and any other issues that you think may be important: Discrepant results of the two dosing regimens despite similar exposure to drisapersen, and lack of statistically significant results on secondary endpoints.

Are there any questions regarding the wording of this question? Are there any questions specifically about the wording of this question?

(No response.)

DR. DUNN: Dr. Alexander, as we begin these questions, I'll just remind the committee of some of my opening comments, that we bring to you in particular today these questions to help us wrestle, if you will, with the issues surrounding the inconsistencies within study 1 and 2, as well as the inconsistencies that we see between study 3 and study 1 and 2 taken together.

So just to ground the discussion of where we're hoping you'll go with this, those are the big picture issues that we're looking for your assistance with today. And I think you'll find the questions open the door for you to approach that in whatever way you think most appropriate.

DR. ALEXANDER: Thank you. So if there are no questions regarding the wording of this question, we'll just move to open discussion. Dr. Nuckolls?

DR. NUCKOLLS: Yes. I just wanted to ask for clarification on exactly what is the difference in the regimen from the continuous and intermittent. It seems there was a period of time. Is it two weeks when they're off with the intermittent? Four weeks? Okay.

To follow up on that, what data is there of the half-life of drisapersen in skeletal muscle tissue?

DR. ALEXANDER: Can the sponsor field that, and maybe just very briefly address the first question, too, which was the difference in the two dosing regimens.

DR. FUCHS: Our best estimate of half-life in muscle tissue of drisapersen is about 12 weeks. The difference in the regimens was, I believe, that everybody got what was considered to be a loading dose, which is double dose for three weeks. Then the continuous regimen then continued to get weekly injection. The intermittent regimen went in the ensuing -- there were 12-week cycles. In 8 of the weeks, it went 2-1, 2-1, 2-1, 2-1, and then 4 weeks

off.

So the difference really is that there were two 4-week holiday periods, and one of those two 4-week holiday periods occurred just immediately prior to the 6-minute walk distance test. It wasn't until much later that exposures became similar as measured in plasma. And we speculate, as we said earlier, that it was that holiday. You have to really be driving dystrophin production to be driving performance.

DR. ALEXANDER: Thank you. Dr. Farkas?

DR. FARKAS: I'm not sure this is the most major point, but as long as the question was asked, perhaps we were wrong about the cycles, and certainly perhaps I don't know it quite well.

DR. TANDON: No. My understanding is --

DR. ALEXANDER: Can you introduce yourself first, please?

DR. TANDON: My name is Veneeta Tandon. I'm the clinical efficacy reviewer at FDA.

My understanding is in study 1, the intermittent regimen was a 10-week cycle with

twice-weekly dosing on week 1, 3, and 5, and once-weekly dosing on week 2, 4, and 6. And there was no dosing between 8 and the 10th week.

DR. FUCHS: I apologize. I stand corrected. I imposed an extra 2-1. That is the correct version.

DR. ALEXANDER: Thank you.

Dr. Temple?

DR. TEMPLE: The sponsor may also want to comment. The endpoint was at 26 weeks, but there were tests at other weeks, too. What would you expect the different dosages to do with them? There were multiple exercise tests.

DR. FUCHS: Yes. If we could have slide 1 up. Here, I believe, it represents the complete data in the first 13 weeks. And Dr. Tandon pointed out that's only 4 weeks of holiday after a 3-week loading dose, 6 weeks of treatment, and 4 weeks of holiday. And then you can see the complete set of data.

I think one of our key considerations is these are relatively small trials, and looking at

endpoints within trials between arms and from time point to time point becomes very, very difficult.

DR. TEMPLE: But for that first 13 weeks, the dosages are pretty similar?

DR. FUCHS: Except for the 4-week holiday.

DR. TEMPLE: So there's a 4-week holiday before that first test?

DR. FUCHS: Yes. And overlapping confidence intervals at the 6-minute walk distance evaluation point.

DR. ALEXANDER: Dr. Bastings?

DR. BASTINGS: Yes. Maybe try to address the question of exposure. May I could ask the sponsor if they have the slide showing the exposure with the continuous regimen and the intermittent regimen in study 1.

DR. FUCHS: We just had it on our screen, AND we'll bring it back. While we're doing that, we can look at slide 3 up, which is a model of continuous and intermittent exposure in study 1. And here you can visualize what we model the differences to be.

DR. BASTINGS: So I would say the exposures look quite similar.

DR. ALEXANDER: Thank you. Are there further slides coming from the sponsor?

DR. FUCHS: I think at this point we've --

DR. ALEXANDER: Thank you. Thank you very much. So we'll move to -- are there clarifying questions regarding this first question being posed to us? Dr. Bagiella?

DR. BAGIELLA: Yes. So what was the reason why you chose these two different strategies of treatment? What did you expect? Why did you choose these two different type of administration of the drug? Why did you design the trial in this way?

DR. FUCHS: Intermittent and --

DR. BAGIELLA: Yes.

DR. FUCHS: Well, GSK, I believe, in consultation with Prosensa, chose to investigate the two different strategies to mitigate potential side effects of phosphorothioate oligonucleotides.

DR. ALEXANDER: Thank you. So it was for

safety concerns, then?

DR. FUCHS: Yes.

DR. ALEXANDER: Thank you.

Very good. So now let's proceed to discussion of this first question.

Discuss the strength of efficacy evidence provided by study 1 with particular consideration of the following issues and any other issues that you think may be important: Discrepant results of the two dosing regimens despite similar exposure to the study drug, and lack of statistically significant results on secondary endpoints.

Dr. Bastings?

DR. BASTINGS: Maybe I could add to that question that I would like the committee also to consider the baseline imbalances in a number of variables that may have had an impact on the study result.

DR. DUNN: Dr. Bastings, did you want to put up a slide?

DR. BASTINGS: Yes. Maybe if you could put up slide 6 of the FDA efficacy presentation. Yes.

This is a slide that compares the baseline 6-minute walk test, the rise time, and so on, where you can see fairly large differences in some of these variables between the treatment groups.

DR. ALEXANDER: Dr. Mielke?

DR. MIELKE: I think that question was asked earlier, though, and it was on this study. When you did adjust for, say, the baseline 6-minute walk test, the results stayed the same or what? I think that was asked a little bit earlier. Was it for this specific study?

DR. ALEXANDER: Yes. There was a question to the FDA previously. I don't know if the biostatistician would like to address this again, but this is again revisiting this question of whether, after adjusting for these baseline differences, one still sees the same efficacy difference.

Dr. Bastings?

DR. BASTINGS: Yes. Just one comment. I would like our statistician to also discuss whether doing a study where we adjust for these variables

can fully correct the imbalances that you can have at baseline.

DR. ALEXANDER: So two questions for the biostatistician. First, when these were adjusted for, did the results differ? And then secondly, to what degree does adjusting for them account for concern about potentially confounding?

DR. YAN: For both questions --

DR. ALEXANDER: If you can state your name first and appointment.

DR. YAN: My name is Sharon Yan. I'm the statistical reviewer of this submission. And when adjusting for the difference and they look, and also looking at the baseline, it doesn't make much difference. There's no significant difference no matter how you analyze it.

DR. ALEXANDER: Thank you. And then the second question was about the degree to which that type of adjustment can take care of potential confounding.

DR. YAN: I can't comment on how much that the adjustment can account for that. But when you

look at the results, it seems that the result for the study 1 for the continuous regimen efficacy is kind of consistent. We don't see the substantial difference when analyzing a different way. But for the intermittent, we don't see the efficacy there.

DR. ALEXANDER: Thank you.

Dr. Bagiella?

DR. BAGIELLA: I would like to see whether either the FDA or the industry can clarify the discrepancy for the secondary endpoints. On slide number 7 from the FDA, it seems that there is a consistent lack of efficacy for study 1 on any of the secondary endpoints, both in the continuous and intermittent arm.

On slide CE-47 of the industry in the forest graph, it seems like -- and they said -- there was a consistent, although not significant for every measure, tendency of the drug being better than the placebo. How come these two are completely the opposite?

DR. ALEXANDER: Please, yes. And if you could repeat the question also. Thank you.

DR. FUCHS: I think the question calls for a comment between the difference in perspectives on the agency's and BioMarin's view of the secondary endpoints of the 117 study. Our analysis, if we could have slide 1 up -- I'm sorry, if we could have the screen slide up -- our analysis looks at the ambulatory lower extremity motor function outcome variables.

We didn't include on this slide, and the agency may have commented on, other secondary endpoints that I mentioned earlier. We did not expect to see vital capacity improvements. These patients are relatively normal. Dystrophin is not a force transducer. We didn't expect muscle strength to be improved.

So if you categorize and dichotomize, better/ worse, and you include everything, I believe you get the agency's analysis. I think if you look at the expectation from improvement in lower extremity function based on where this population is in its evolution, you get the results on the screen.

I don't believe there's a difference in analysis as much as interpretation of the analysis.

DR. BAGIELLA: The estimate of the effects and the confidence intervals are different. So what was the analysis the FDA conducted on this data, on slide number 7?

DR. TANDON: I think there is a trend towards --

DR. ALEXANDER: Can you identify yourself, please?

DR. TANDON: Sorry. My name is Veneeta Tandon. I'm the clinical efficacy reviewer at FDA.

I think the results are not different between the sponsor and us. It's just how we present the data. We have presented the data as they were collected, and the sponsor and our analysis both show that there was a trend in front of continuous drisapersen for most endpoints.

The only additional endpoint I show is the muscle strength that there sponsor didn't have. And the sponsor has done a statistical manipulation of the data to make all the endpoints comparable

because the units are different. So they have divided the endpoints by the standard deviation, and they presented that way.

The second difference is that they report velocities in their data set, and I have not reported rise time velocities and four-stair climb velocities. So the p-value is a little different because of that because they have tried to normalize all the endpoints to a single unit by dividing it by the standard deviation.

DR. ALEXANDER: Dr. Ovbiagele?

DR. OVBIAGELE: Thank you. I'm sorry. I just wanted to revisit the imbalance in the baseline variables because I'm a little perplexed.

Dr. Tandon, you had mentioned previously that it was too small to actually adjust all those different variables. Then, Dr. Yan, you mentioned that it was adjusted for. So I just wanted to just be consistent in terms of was it adjusted for? Was there still an advantage or a benefit in study 1?

The second issue is the issue that Dr. Bastings mentioned, which is the issue of

unmeasured confounding. Just consistently, when you look at the various variables, the continuous group is just better. They just seemed better at baseline. And I just wonder that even if we were able to adjust for those things, they just seem, for everything, much better.

DR. YAN: My name is Sharon Yan. I'm the statistical reviewer. I just want to clarify one thing that I previously said, that for adjusting those baseline characteristics, we did adjust -- the baseline walking distance is included in the model, and we did look at the age difference. But other things like rise from floor and four-stair climb ascent, they were not. We didn't look into those aspects as the study was small.

DR. TANDON: This is Veneeta Tandon again, clinical reviewer from the FDA. I would just like to clarify what Dr. Yan just said, that only 6-minute walking distance and age were included in the model and adjusted for that. But what I list as baseline imbalances are other factors like the

ability to jump up and rise time and the ability to hop with clearing foot from the heel. And those were not included in the model.

DR. ALEXANDER: Dr. Farkas and then Dr. Temple.

DR. FARKAS: Yes. I think we've clarified the answer to that question. I talked with the supervisory statisticians, too, and I don't want to try to be the statistician. But the one thing that they said that I can communicate to you is it's complicated. It's not that simple.

So I think that this is something that we're going to certainly think about. But I think that going back -- the message that I get from them is going back and trying to do these after-the-fact corrections, that's actually not something that's likely to be reliable.

DR. ALEXANDER: Thank you.

Dr. Temple, and then perhaps we'll move to the second question.

DR. TEMPLE: Dr. Dunn has a comment, too. But I'd just make the point -- maybe everybody

understands this -- but the question isn't whether there were baseline differences between the two groups. The continuous group was healthier in a number of ways.

But remember, what we're looking for is change from baseline here. So the question is whether being better at baseline leads to a greater likelihood of improving. And that's what I think their analyses were doing, and they didn't find anything like that. The statisticians and others can correct me if I'm wrong.

So a difference between them wouldn't matter if everybody improves or is likely to improve by the same amount. It wouldn't make any difference. And I don't think we think there was any evidence that being better makes you improve more.

So it isn't whether there was a difference at baseline. There was. But whether that explains the results is the question they had to answer.

DR. ALEXANDER: Thank you.

Dr. Mielke, and then we'll move to question 2.

DR. MIELKE: Just again with question 1B, lack of statistically significant results on secondary endpoints, I'm a bit confused as well on that with Dr. Bagiella.

Based on the sponsor's analyses, there's not much of a lack of statistical significance, and it's quite favorable compared to what the FDA slide is showing here. So again, when we do go to vote on it, how do you want us to answer this? What do you want us to focus on?

DR. ALEXANDER: It sounds like some uncertainty regarding whether indeed or not there are the same results from the sponsor and the FDA regarding the secondary endpoints for study number 1.

DR. TANDON: This is Veneeta Tandon, clinical reviewer at the FDA.

Our analysis is based on what the sponsor has submitted in their study report, and we try to just look at that. And the sponsor has converted it to velocity, and they have tried to standardize all the endpoints by dividing it with the standard

deviation to normalize it for a single unit because each endpoint has a different unit, so in order to present that in an forest plot, they have tried to standardize it. And I think that changes the p-value.

DR. BAGIELLA: We're not talking about the p-value -- sorry, because this is continuation of what I can't understand, either. And when you standardize by the standard deviation, the standard deviation is always positive.

So it's the numerator here that is going in different directions. Your numerator is going negative. Theirs is going positive. Whether you divide or not for any positive value, it really doesn't matter. Right?

So why is yours negative and theirs is positive if you're using the same data? If you take a difference, the difference either go one way or the other. It can't go in two different ways.

DR. TANDON: This is Veneeta Tandon, the clinical reviewer at FDA. Our data represents what the true study endpoint was and the way it was

collected, and the difference from drisapersen and placebo. But the sponsor can explain the statistical normalization they have done to present the way they present.

Ours is just a simple report of how the endpoint was collected and, per protocol, how it was supposed to be reported in the study report. And we do not normalize all the endpoints. So ours is just looking at the protocol and doing the analysis based on that.

DR. ALEXANDER: Thank you.

Does someone from the sponsor want to briefly address this question of different direction, if not magnitude, of secondary endpoints for study 1?

DR. FUCHS: I'm going to have Dr. Wilson, our statistician, address it. It might pertain to the difference between velocity and the rise time.

DR. WILSON: Hello. My name is Dr. Rosamund Wilson. I'm a consultant statistician working with BioMarin. I have been working on the drisapersen program since 2010, and I have no financial

interest in the outcome of this advisory committee.

The assessment of secondary endpoints in our presentation is based on a conversion to velocities. That means that if somebody takes 5 seconds to rise four stairs, we've said they take 0.8 seconds per stair to rise. So that's one of the differences in the presentation. If we put slide 1 up, that's the presentation that you're referring to.

In the FDA presentation, I believe the data presented is the week 48 data. And if we put slide 2 up, we have the presentation of the secondary endpoints, the treatment differences based on the absolute values from our study report.

DR. ALEXANDER: Thank you. And while we may not be able to see these side by side, it looks as if they align. That is, these are consistent with the data that we saw from the FDA?

DR. TANDON: Yes.

DR. BAGIELLA: This is week 48. The FDA's slides is at week 24.

DR. TEMPLE: But they have similar

properties. Three of them are bordering on significant, and three are in the right direction but not quite significant.

DR. WILSON: So just to confirm, yes. For the velocities, the negative value is an improvement because a reduction in that --

DR. DUNN: Yes. I suspect if you showed your slide at week 24, your presentation on this matter would be the same as ours. We're presenting the secondaries as they align with the primary endpoint.

Particularly, Dr. Alexander, if there's no other specific commentary now, since you're talking about going on to question 2, and given the discussion that we've heard about question 1, I thought it might be helpful just to rephrase for the committee, in a slightly different manner, what we're trying to get at here, what the review team has encountered during the conduct of their review.

Study 1 has, on face, a positive result for an arm of the trial. The study is positive in one of its arms. The persuasiveness of that result is

what we're trying to get you all to consider.

We are struck by things like baseline imbalances, and we're particularly struck by other avenues of exploration that may serve to reinforce the persuasiveness of the face result of the study, such as the fact that the other arm has the same exposure, and we do not see a result that would reinforce or support the arm of concern.

Similarly, we look to the secondary endpoints for support, and although we see some trends in some that come near to significance, we see no actual statistical significance in those secondaries, and some of them don't come close.

So these areas that don't provide additional support, we are interested in your assessment of what that does to the persuasiveness of the face finding of positivity in the continuous arm. I hope that maybe helps rephrase the discussion a little bit.

DR. ALEXANDER: Thank you.

Is this a question of clarification?

DR. GONZALES: No.

DR. ALEXANDER: Okay. I'd like to move on to question 2. I think we need to move on, in the interest of time. Thank you.

So question 2 is what overall impact do the issues discussed in question 1 have on the persuasiveness of study 1? And so this is a voting question.

For voting questions, we will be using an electronic system. When we begin the vote, the buttons on your microphone 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 you 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 voted will state their name and vote

into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

I'd like to just briefly try to summarize some of what I heard for the discussion around question 1. It was noted that there are baseline differences that are noteworthy between the two treatment arms in study 1.

There was discussion regarding the adjustment as to whether there was adjustment for these baseline characteristics. My understanding is that both age and baseline walking distance were adjusted for, but not all factors that were different at baseline were adjusted for in the models. There was the point raised that even adjusting for baseline differences may or may not address concerns about residual confounding.

The adjustment for baseline differences in study 1 did not change the magnitude or direction of the main findings. These results were statistically significant for the continuous but

not the intermittent treatment arms. Both arms achieved similar plasma concentrations.

The basis for differences in the secondary endpoints was mixed. It sounds as if both FDA and sponsor agree regarding the quantitative results, but there is somewhat different interpretations regarding these.

The sponsor performed a statistical manipulation to make the endpoints more comparable because the units are different and they report velocities, which the FDA did not. The p-values may be slightly different because these endpoints were normalized.

But overall, there's no disagreement between the sponsor and the FDA regarding the magnitude of the secondary endpoints. There was a trend towards favorability, particularly for the continuous treatment arm, for many outcomes.

Is there anything else on the record briefly summarizing the discussion from study question 1?

(No response.)

DR. ALEXANDER: Great. So we'll move to

study question 2. Once again, this is a voting question.

What overall impact do the issues discussed in question 1 have on the persuasiveness of study 1? Do they, A, strengthen the persuasiveness? B, weaken the persuasiveness? Or C, have no effect?

So we'll move to questions before we vote -- or, I'm sorry, we'll move to discussion of this question before vote. Dr. Mielke?

DR. MIELKE: Sorry. Just a clarification. We talked separately in 1 about A and B, and we could have differing opinions on A versus B. But you want us just to give you one summary for the whole thing?

DR. DUNN: That's correct. We're asking you to integrate the issues that we've raised for discussion in this question in terms of your assessment of the persuasiveness of the face finding in the continuous arm.

DR. ALEXANDER: Other comments about this question? So if there's either questions regarding

the wording of this question or anything that you wish to state on the record about this prior to the vote?

(No response.)

DR. ALEXANDER: Okay. Very good. So we'll move to voting on this.

(Vote taken.)

DR. ALEXANDER: Thank you. So the vote is closed. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and explain the rationale for their vote.

DR. BAUTISTA: Sorry. Before we do that, I'm going to go ahead and read the vote into the record. One member of the committee voted for A; 9 members of the committee voted for B; 7 members of the committee voted for C.

DR. ALEXANDER: Thank you.

So we'll begin with Dr. Estrella. If you'd like to begin and read into the record; please tell us your name, your vote, and explain a brief rationale.

DR. ESTRELLA: Hi. My name is Michelle Estrella. I voted for B, weaken. My rationale for this was mainly surrounding discussions on question -- or I guess the discussion 1.

There remains a concern for residual confounding, given the baseline imbalances with regards to characteristics that would favor the continuous arm, which was the only arm which showed a potential effect of the drug. I'm trying to read my notes here.

This is also further emphasized by the fact that both the intermittent as well as the continuous arms had similar drug levels and still disparate results.

DR. FOLEY: Reghan Foley. I voted for C, and my rationale was that I thought that taking together A and B, I felt probably the population of patients on the continuous versus intermittent were probably at baseline a bit distinct. Then secondary endpoints can be a challenge in this population. I thought that the primary endpoint was somewhat convincing.

DR. NUCKOLLS: Glen Nuckolls. I voted B. I felt that given the similar exposure levels and the relatively long half-life of the drug in muscle tissue, that we would expect to see similar outcomes in the two parts of the trial. And as the FDA presented, the secondary outcomes lack statistical significance.

DR. LEVINE: My name is Rodney Levine. I voted B, and the reasons were essentially the same as Dr. Nuckolls just mentioned.

MS. GUNVALSON: My name is Cheri Gunvalson, and the second lady that spoke is really my feelings also.

DR. HOFFMANN: Richard Hoffman. I voted C. I still feel that the kinetics of the drisapersen is changed when you stop the drug for 4 weeks, and I think that affected study 2. And I also believe that the endpoints for most of the secondary endpoints were in favor of drisapersen.

MR. CASSIDY: Christopher Cassidy. I said B, for the same reasoning as Dr. Nuckolls and Dr. Levine, in that I feel that both the regular

and the intermittent had about the same amount of exposure, and I would expect similar results.

DR. GREEN: Mark Green. I voted B, for the same reason, that the area under the curve was fundamentally the same, the results quite different. Perhaps a study, given the long half-life, needed to be double in length.

DR. ONYIKE: Chiadu Onyike. I voted B, for a drug with a candidate mechanism that has biological results should converge if exposure is about equivalent, and we're not seeing that.

DR. GONZALES: Nicole Gonzales. I voted A. Since the drug exposure in the two treatment groups were the same, it makes the most sense to me to evaluate the data for the two treatment groups as one group; in the table 9 that was provided in Dr. Tandon's written clinical review. In that case, the point estimate is no longer statistically significant but is still clinically relevant. So the treatment effect appears to be attenuated.

In terms of the subgroup analysis, most of the point estimates were still in favor of drug,

but not statistically significant. So everything to me supported the potential for drug, perhaps not in a statistically significant way but in a clinically relevant way.

DR. ALEXANDER: Caleb Alexander. I voted B, primarily for the reasons stated regarding the absence of similar efficacy despite similar plasma concentrations and also the absence of consistent and robust secondary endpoints.

DR. OVBIAGELE: Bruce Ovbiagele. I voted B as well. A similar reason as well to Dr. Alexander, and also recognizing the fact there was an inability to fully and reliably correct for the differences in baseline prognosticators.

DR. ZIVIN: Justin Zivin. I voted C because this is a relatively small and noisy data set. And secondary endpoints are called that for a reason. They're not the prime thing you're going after, and they can be helpful if they are pointing in the right direction. But if they're pointing in the wrong direction, you don't necessarily know what it means.

DR. BAGIELLA: Emilia Bagiella. I have a similar argument. I think this was a phase 2 study. They had two arms, it was not clear to me, that were the same and could go in different directions. And again, the secondary endpoints probably don't have a lot of weight in this context. So I thought that they didn't quite impact on the overall result.

DR. MIELKE: Michelle Mielke. I voted C, no effect. I thought there was a good point about the discrepant results of the two dosing regimens, which likely potentially weakened the strength of efficacy. However, when looking at the secondary endpoints, if anything, I thought they potentially strengthened it, so evening it out, and overall no effect.

DR. KESSELHEIM: Aaron Kesselheim. I voted C, largely for similar reasons to Drs. Zivin and Bagiella. Although I am a little bit concerned about the baseline imbalance, I thought that overall the secondary endpoints are -- it's a very small study, and the secondary endpoints can be

variably measured. So I voted C.

DR. ROMITTI: Paul Romitti. I voted B, and I voted B for reasons mentioned in terms of differences in outcome with essentially the same dosage, just in different fashions. Also, while the secondary endpoints and the small sample size can cause noise, I would have expected to see a better agreement between the two, between the primary and the secondary endpoints. So for those reasons, I voted B.

DR. ALEXANDER: Thank you. That marks the conclusion of discussing question number 2. We'll move to question 3.

Discuss the strength of efficacy evidence provided by study 2, with particular consideration of the following issues and any other issues that you think may be important:

A, lack of statistical significance of the primary outcome, p equals 0.07 on intention-to-treat analyses, p equals 0.23 on per protocol analyses;

B, the 3 milligram per kilogram group

numerically inferior to placebo;

C, the 6 milligram per kilogram group numerically inferior to placebo for most secondary endpoints.

So this question is now open for discussion, unless there are clarifying questions regarding this. Dr. Hoffmann?

DR. HOFFMANN: I just had one question about clinical significance. The reviewer called the .07 near significant, I believe, in her review, and I just wonder how tightly does the FDA hold to the .05 levels for significance?

DR. ALEXANDER: Dr. Temple?

DR. TEMPLE: Yes. Well, it's a little bit of an historical artifact, and one could ask where that .05 came from. But as a general matter, we think a study should be significant at .05 or .025 one-sided, which is really what it is, to be considered statistically significant.

That doesn't mean we go crazy if it's .052. So there's a certain amount of flexibility. But in general, we expect it toe significant at that

level.

DR. ALEXANDER: Dr. Zivin?

DR. ZIVIN: There's nothing magic about .05. We're talking about a fatal disease that has no treatment. And I believe that under those circumstances, there should be some leeway to go up a little bit.

DR. ALEXANDER: Yes. I think one thing that I noted is that I believe the removal of one patient changed the 24-week results from p 0.07 to 0.23, if I recall. So I think that highlights for me both the small sample sizes as well as the sensitivity of the results to particular influential data points.

DR. DUNN: Right. Just to reinforce that, I think that what you're seeing here in the theme of the first question, and this question as well, is the notion that we have data that either nominally demonstrate or suggest efficacy.

What we look for is we try to probe those data and see how resilient they are. And I think what we're doing is sharing with you some of the

issues that we encounter that have us trying to sort out how resilient that finding is.

So we recognize that .07 is close to .05. We understand that. It's got our attention, and we take Dr. Zivin's point as well. The issue here is to share with you the things that we're trying to use to contextualize that result and sort out, again, how resilient it is.

We're asking the committee to think about that as well, and get a sense of what that does to the persuasiveness of the finding.

DR. ALEXANDER: Are there comments among the committee regarding this difference between the 3 and 6 milligram per kilogram group? How do you interpret that or the fact that the 3 milligram per kilogram group was numerically inferior to placebo?

DR. HOFFMANN: My interpretation is that the 3 milligram per kilogram just was not an effective dose in any of the studies and shouldn't even be considered.

DR. ALEXANDER: Thank you. Comments regarding the 6 milligram per kilogram group and

its being numerically inferior to placebo for most secondary endpoints? Yes, Dr. Unger?

DR. UNGER: Unger. Hi. I just want to mention -- I'm trying to draw out a little bit of discussion here because you're going to be asked to vote, and then you're going to have to explain your vote. But once you cast your vote, you won't have the benefit of the influence of other minds.

So the discussion was great on question 2, but it's best to have that discussion before you vote so people can debate and think about it and maybe change their mind. So I'm just trying to get people to pretend you voted and discuss. Thank you.

(Laughter.)

DR. ALEXANDER: Yes. Dr. Gonzales?

DR. GONZALES: In the spirit of that comment, I'll just throw out an opinion about C. The first study, while promising and very much hypothesis-generating, was very small and probably under-powered, as both of these studies, I think, were.

So in terms of the 6 milligram per kilo group being inferior to placebo for most of the secondary endpoints, I think now we're just getting more data. And so we're actually seeing that what we saw in the first study may not actually be reality.

So for me, this just provides more evidence that we've got two small, underpowered studies, and not yet sure what to do with this data.

DR. ALEXANDER: Dr. Bagiella?

DR. BAGIELLA: At the time that these studies were designed, I would think that they were powered to find at least a signal of efficacy. Right? Was the dose reduced to half, again, for safety issues?

DR. ALEXANDER: This is maybe a question for the sponsor. What was the rationale for the 3 milligram per kilogram dose? And I think it would also be an opportunity to emphasize or clarify that these studies were adequately powered for the primary endpoints.

DR. FUCHS: Yes. I believe that study 1

does have a statement, I think, in the statistical plan, if not in the protocol, about the power of the study being to detect an effect of 1, which I believe would be the number of meters divided by the standard deviation of the change from baseline. I think that's right.

DR. ALEXANDER: I'm sorry. That's study 2 which we're discussing.

DR. FUCHS: I just mentioned study 1. And I don't believe study 2 had a formal statement. Let's leave it that I don't believe it had a formal statement. It was intended to evaluate a lower dose and whether that was effective.

DR. ALEXANDER: Just to clarify, so study 1 was powered -- can you just clarify again what the studies were powered for study 1 and study 2?

DR. FUCHS: I believe my team is confirming that study 1 had a statement of the planned sample size being based on -- the study being powered to detect a standardized effect size of 1. And study 2 did not have a prospective statement of a planned effect size.

But in reality, all studies have some power, and the magnitude that you observe is -- you have to interpret the p-values. I think that's been pretty much the standard of discussion so far.

DR. ALEXANDER: Dr. Farkas?

DR. FARKAS: I was wondering if I could get up slide 10 from the FDA presentation. And again, I think to stimulate discussion, part of what the team was doing, we of course spent a lot of time looking at the results and trying to figure out how to interpret things that might be uncertain.

So there's 24 weeks of drug treatment and then no drug treatment. And the spread of those lines during that second 24 weeks, we spent a lot of time talking about, and perhaps the committee would want to spend some time talking about.

DR. ALEXANDER: Thank you. So maybe you can leave this up, and we can discuss for a few minutes these data, the distribution of the data across these three arms -- in red, the 6 milligram per kilogram per week; in green, the 3 milligram per kilogram per week; and in blue, the placebo. And

once again, after 24 weeks, there was no continued treatment.

Dr. Onyike?

DR. ONYIKE: What the slide does not show is how the number of subjects changes as we go along from the beginning to the end. I believe that especially in small studies, attrition changes the statistical power.

DR. FARKAS: This is Dr. Farkas. I think Dr. Tandon said that either there were no dropouts or very few. We could confirm that, but I think there might have been no dropouts. No dropouts.

DR. ALEXANDER: Yes. Dr. Estrella?

DR. ESTRELLA: Hi. I just had a question. So there were concerns in study 1 with regards to differences in baseline characteristics. I don't recall if there was some discussion in terms of similarities in baseline characteristics by treatment group for study 2.

DR. ALEXANDER: So the question is, were there differences in baseline characteristics between the three arms in study 2.

DR. ESTRELLA: Yes. I'm just trying to reconcile the inferior or less impressive effect of the 3 milligram dose versus placebo.

DR. TANDON: My name is Veneeta Tandon. I'm the clinical efficacy reviewer. Can we pull up backup slide number 2? This slide shows that the 3 milligram per kilogram per week group had certain characteristics that appeared worse than the placebo group.

For example, the baseline 6-minute walking distance, the percentage of subjects is fewer; the baseline rise time, there's a percentage difference; and the use of steroid treatment, although that's not such a large number; and then the ability to rise from floor without Gower's maneuver. There were no subjects in the 3 milligram per kilogram group who could do that, and there were 13 percent in the placebo group.

DR. ALEXANDER: So it feels as if some of the differences that we see between the 3 milligram -- that some of the reasons that the 3 milligram per kilogram per week group may have

done worse than the placebo is due to baseline differences between them? I guess that's a question that's being raised.

Dr. Farkas?

DR. FARKAS: Yes. I think one thing is there's a certain subjectiveness to trying to look at the baseline imbalances. I think it's definitely worthwhile to call this up and try to investigate more, but I think one reason that we didn't talk about it more is -- Dr. Tandon had highlighted where there were some baseline imbalances that looked like they favored the 6 milligram per kilogram over the placebo arm, too.

Ultimately, in some sense, it's a little hard to know what all the baseline imbalances mean. We have the observations from a number of different studies as another bigger picture way that we're looking at it. But anyway, certainly appreciate it that we took a look at these.

DR. ALEXANDER: Dr. Mielke and then Dr. Onyike.

DR. MIELKE: My interpretation, looking back

at slide 10, which we were just looking at, suggests that the 6 milligram group supports the first study, but that the 3 milligram group probably wasn't a high enough dose and so therefore is no different from placebo.

But the part that worries me is just the removal of the single patient that reduces that p-value. But by looking at the graphs the way they are, we can't see any of the data points. And so I'm just wondering if there are any other outliers that could have even pulled it back to being, I guess, closer to significance or could have affected it as much as this one is.

DR. ALEXANDER: So there's a question about whether there are other influential outliers that could have affected the results either in the same direction or a different direction than the one example that we've been provided, where the removal of one patient changed the p-value from 0.07 to 0.23.

DR. TANDON: This is Veneeta Tandon, clinical efficacy reviewer. I do not believe so.

DR. ALEXANDER: I think Dr. Onyike was next, if that's okay, and then we'll hear from Dr. Temple or Dr. Bastings.

DR. ONYIKE: So if we can pull back Dr. Tandon's backup slide 2, please. So going back to the interpretation of group comparisons at baseline, if we are thinking in terms of things that we believe might predict the future, yes, it would seem to favor the treatment group.

But if we look at indices of how the patients are in the here and now, one could see it in the reverse. So for example, if you look at the baseline 6MWD or at the baseline rise time, or any other factors other than age and continuous regimen, one might argue that the placebo group is better, really, than the 6 milligram group. So I just wanted to say that.

DR. ALEXANDER: Thank you.

Dr. Bastings and Dr. Temple?

DR. BASTINGS: Yes. The point I wanted to make, the patient that got removed in the analysis that changed the p-value to .024 or something like

that, the patient was not removed because he was an outlier. The patient was removed because that was the per protocol analysis. There was a protocol variation, unblinded. He wasn't blinded. So the reason is not that he was an outlier.

DR. ALEXANDER: Thank you. So just a clarification for the reason the patient being removed, it was because he was unblinded, not because he was an outlier.

Comment from the sponsor?

DR. FUCHS: Dr. McDonald knows the patient. I don't believe the patient was unblinded. I think there was an unblinding code broken in the emergency department. Maybe it's a small nuance, but --

DR. MCDONALD: Just a comment. The patient and family was never unblinded to the treatment, nor was the investigators unblinded. It was simply a clinical evaluator that received a fax, and the clinical evaluator was unblinded. They removed themselves from any further contact or participation in the study for that individual

patient.

DR. ALEXANDER: Thank you very much.

We'll have one or two more comments, and then I'd like to move to the voting portion of this question, and then we'll take a break, just to stay on track. Dr. Temple?

DR. TEMPLE: I don't want to sound like a broken record too much, but it's worth remembering. This isn't which group is healthier or which group is better. It's which group is more likely to change over a period of time.

Whether those properties predict that, I think is quite uncertain. So I'm not sure what these imbalances would mean. I think that was something like your comment.

DR. ALEXANDER: Dr. Romitti?

DR. ROMITTI: Yes. A very simple statement. We're all aware of this, but I just thought I'd bring it up again. When we talk about this, and I guess the struggle I have with the very small sample size in the study and try to conclude from this, a movement of one person from one of these

categories, for example, from above or below 400 meters, will change these percentages considerably.

Looking at these percentages, they're very unstable. So they're very volatile. And I just think we have to caution ourselves -- well, I'll caution myself, at least -- to say I can't put a lot of support in this for actually the study outcome. I think the numbers are too volatile.

DR. ALEXANDER: Thank you. I think I'd like to move on. We'll move on to the voting portion of this question, although it does look like we got discussion going, which is good.

So next is question 4, which is, what overall impact do the issues discussed in question 3, I believe this should read, have on the persuasiveness of study number 2? In other words, what overall impact do the issues that we just discussed regarding study number 2 have on the persuasiveness of study number 2?

Do they strengthen the findings, strengthen the persuasiveness of the study? Do they weaken

the persuasiveness of the study? Or do they have no effect on the persuasiveness of the study?

Shall we discuss further before we vote? It looks like there are a few more hands. So Dr. Foley?

DR. FOLEY: I just want to make a comment. Looking at the patients that were on continuous steroids, you had 100 percent of the 6 milligram per kilogram per week on continuous steroids, 88 percent of the 3 milligram per kilogram per week, and 94 percent of placebo. So that may be affecting, potentially, the results.

DR. ALEXANDER: Thank you.

Dr. Gonzales?

DR. GONZALES: Yes. Just a clarification of the question. So the overall impact do the issues discussed in question 2 have on the persuasiveness of study 2, do you mean in terms of whether we feel that the drug is actually beneficial or not, or just the outcomes of the study in general?

DR. ALEXANDER: Dr. Bastings?

DR. DUNN: I'm sorry. Could you repeat the

question?

DR. GONZALES: Basically, is this question asking, does the totality of the data at this point -- how does it affect the way I think of the drug treatment, or what do I just think of the study outcomes in general?

DR. DUNN: This voting question focuses on what you think about the persuasiveness of the efficacy evidence coming particularly from study 2.

DR. GONZALES: From the study. Thank you.

DR. DUNN: You'll have a chance to comment later in the questions on how you view the totality of these studies together.

DR. ALEXANDER: Dr. Estrella and Mr. Cassidy, and then perhaps we'll vote. Mr. Cassidy?

MR. CASSIDY: Just to clarify, continuous use of steroids, does that mean as opposed to intermittent, like every other week? Or does that mean no steroids? Because if I recall, to be a subject in this, you had to be on steroids for I think it was up to 6 months before the trial. I just wanted to clarify.

DR. ALEXANDER: Thank you. So if the sponsor or someone from the FDA could clarify what was meant by continuous use of steroids?

DR. FUCHS: Intermittent is classified as -- intermittent is on the weekend or every other week. You're still on corticosteroids. Everybody is on corticosteroids.

DR. ALEXANDER: Thank you.

Are there any further questions about this question before we vote, or further discussion?

(No response.)

DR. ALEXANDER: Great. So we'll then move to voting. The question, once again, is what overall impact do the issues that we just discussed in question number 3, that is, the issues regarding study number 2, have on the persuasiveness of study number 2 with respect to the efficacy endpoints? Do they A, strengthen, B, weaken, or C, have no effect?

I'm also going to summarize everything that I heard about question 3, just for the record. There was a question regarding the threshold of p-

value, 0.05, and that's a generally accepted threshold, but there's a certain amount of flexibility.

There was a reiteration that the 24-week endpoint was negative for both treatment groups, p 0.07, and the removal of one patient changed that to 0.23, highlighting the degree to which certain data points could be influential. The patient was removed because there was an unblinding code broken. The patient and family were not unblinded.

There was a question regarding whether there could be other influential outliers, and the statistical reviewer at the FDA reported that that's not the case.

Three milligrams per kilogram was felt to be an ineffective dose by someone, and therefore not more effective than placebo.

Someone felt that the studies were underpowered and wasn't sure what to do with the data. It was clarified that study 1 was powered to detect a standardized effect size of 1. Study 2 did not have a planned effect size.

There was a review of the slide of the effects over time, and although it didn't depict the number of subjects over time, attrition was minimal.

There were questions about the baseline differences across the three arms in study 2, and the answer was that there were some, although in some cases there were characteristics that appeared worse for the placebo group or these didn't all travel in the same direction.

There was an emphasis that interpreting the effects of baseline differences, imbalances at baseline, is difficult.

A point was made that it's not which group is healthier or which group is better but in which group is there more likely to be change over time, and I think there's some difference of opinion regarding how clearly one can predict that from baseline differences.

A comment regarding the movement of thresholds of different categories being able to change the baseline percentages a lot, so the

numbers are very volatile. And there was also a mention that the proportion of steroids differed across the arms.

(Vote taken.)

DR. BAUTISTA: The vote is complete for question number 4. I'll now read the vote into the record. Zero members of the committee voted for A and B; 12 members of the committee voted for C -- excuse me. Let me reread that. Zero members of the committee voted for A; 5 members of the committee voted for B; 12 members of the committee voted for C. Thank you.

DR. ALEXANDER: So next, why don't we begin with Dr. Romitti this time. And if you could just state your name and your vote and provide a brief rationale for your vote, and we'll go around the table.

DR. ROMITTI: Paul Romitti. I voted for C. I really don't think these points had an effect. I struggle with the sample size and the study design to make hard and fast conclusions from this, other than the fact that 3 milligrams did not perform as

well as 6 milligrams. Other than that, I have difficulties interpreting the study.

DR. KESSELHEIM: Aaron Kesselheim. I voted C also. You sort of have what you have. These are two very small phase 2 studies with positive to marginally negative endpoints. They're potentially encouraging or potentially not encouraging. I'm not sure that the secondary endpoints have much to add to that.

I think that they have a lot of positives in there, that some people can grab onto a lot of negatives that others can. So overall, I just feel like they're two studies that help lay the ground work around this drug. But beyond that, I can't put that much importance to the 0.07, given the volatility of the number of patients.

DR. MIELKE: Michelle Mielke. I voted C as well, no effect, primarily for the same reasons. I think the sample size is small. There is a lot of volatility. We're just not quite sure exactly what's going on.

In terms of the secondary endpoints, again,

the sample size is small and it's unclear. Again, the only thing that does seem to be clear is that the 3 milligram per kilogram group dosage doesn't work as well as the 6 milligram per kilogram.

DR. BAGIELLA: Emilia Bagiella. I voted C, mainly for the same reasons that I voted C before. I think that this is a phase 2 study. It has to be taken as an early phase study. I don't think that the p-value has any bearing on the result of this setting. And I think that there is signal still for the 6 milligrams. Obviously, there is no signal for the 3 milligrams.

DR. ZIVIN: Justin Zivin. I have nothing to add.

DR. ALEXANDER: Can you state your vote for the record?

DR. ZIVIN: Sorry. It was C.

DR. OVBIAGELE: Bruce Ovbiagele. I voted B. I wasn't really convinced that this was persuasive, not largely because of B and C; that's the issue of inferior to placebo or the issue of the secondary endpoints.

It was really driven by the issue of the statistical significance, and not so much because it was greater than .05, but just because typically what you have is per protocol -- intention to treat; p-values are typically larger than per protocol. And in this case, you had it reversed. It really made me feel as if the efficacy was really not proven here since per protocol seemed to have a larger p-value than the ITT.

DR. ALEXANDER: Caleb Alexander. I voted B. I don't know that it changed my feelings about the persuasiveness tremendously, and I'm comfortable that the 3 milligram per kilogram dose may not suffice.

I think I just weighed a little bit more highly, perhaps, than some the fact that a single data point could be so influential. And I also just would have liked to have seen the secondary endpoints more consistently support the primary outcome, and the fact that some statistically favored placebo also threw me off a bit.

DR. GONZALES: Nicole Gonzales. I also

voted for C. I'd like to echo your comments about the results being sensitive to movement of just one patient.

In addition, the primary endpoint is not significant, although one might argue that it's still clinically relevant. I would have liked to have seen this treatment effect go out to week 48, as in the previous study, but it did not.

The findings in the sum group analysis no longer supported efficacy of the drug, clinical efficacy of the drug. So I felt like overall, it weakened my belief in the study results.

DR. ONYIKE: Chiadu Onyike. I voted C. I subscribe basically to the views expressed by Drs. Romitti, Kesselheim, Mielke, and Bagiella.

DR. GREEN: Mark Green. I voted C. I'm also not terribly bothered by the secondary endpoints, basically, and the sample being imbalanced isn't as meaningful. We're treating people over a lifetime and not over a snapshot. And if the drug isn't useful beyond a snapshot, it's not going to be terribly valuable for us.

Again, I said this before, but I'm still bothered by the fact that the evaluation time is not terribly different from the time the drug reaches a steady state.

MR. CASSIDY: Christopher Cassidy. I voted B, weakens. This didn't persuade me any further. And I was particularly concerned about the study being under-powered and how the removal of a single patient, regardless of the reasons, had such an effect on the p-value.

I do realize that the number of individuals with Duchenne is very small, and then the number that could benefit from a drug used for skipping exon 51. That being said, I just don't feel that the trial was large enough to get any really meaningful idea of its effect.

DR. HOFFMANN: Richard Hoffman. I voted C, no effect. .07 is what it is, and I believe that the results favored drisapersen for most of the secondary endpoints.

MS. GUNVALSON: I'm Cheri Gunvalson, and I voted C also. I don't have much to add. The

3 milligram per kilogram was not an appropriate -- didn't work, and due to the sample size and such, there was no clear measure in the secondary endpoints.

DR. LEVINE: Rod Levine. I voted B. I think that all three points emphasize the lack of resilience and the problem of the small numbers. But I was especially influenced by A, the failure to meet the primary outcome measure, and the extremely large effect of removing a single patient.

DR. NUCKOLLS: Glen Nuckolls. I voted C. With the small sample size, I felt that it was an inconclusive study, and the discussion that we had just reinforced that it was an inconclusive study.

DR. FOLEY: Reghan Foley, and I agree with Dr. Nuckolls. Sample size is small and inconclusive.

DR. ESTRELLA: Michelle Estrella. I voted C, no effect, for similar reasons previously stated. I think the data are very difficult to interpret with the small sample size, as well as,

although we've been instructed not to put too much emphasis on baseline imbalances, there are remaining imbalances that are difficult to interpret as well.

DR. ALEXANDER: Great. Thank you very much for those comments.

We will now take a 10-minute break, so we will reconvene 5 minutes till 4:00. Panel members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. Once again, we'll resume in 10 minutes.

(Whereupon, at 3:46 p.m., a brief recess was taken.)

DR. ALEXANDER: We'll resume where we left off. So we're now moving to question number 5, if everyone can take their seats, please. And this question and the one that follows it, question 6, are structured very similarly to the two previous sets of questions.

So in this open discussion question, we're asked to discuss the evidence provided by study 3,

with particular consideration of the following issues and any other issues that we think may be relevant: A, the lack of statistical significance of the primary outcome measure, p equals 0.42, in a well-powered phase 3 study; and B, the lack of nominally statistically significant results on all secondary endpoints.

So this question now is open for discussion. And as with the previous questions, this is an opportunity for us to talk through our thoughts regarding the efficacy outcomes and how we make sense of them, and how we might do so before moving to voting.

Dr. Romitti?

DR. ROMITTI: I have a procedural question, and so if we can do it. This is directed at the FDA. But in hearing the sponsor talk about looking at the totality of responses and looking across all studies, I don't see that being addressed in any of these questions. And I'm trying to figure out where, if at all, we can address that.

DR. ALEXANDER: So a question for the FDA.

Is there an opportunity to address or discuss what the sponsor has presented as the totality of findings across all of the studies and the clinical development program. Dr. Temple?

DR. DUNN: I think -- well, anyway, I think that the place to perhaps do that would be we provided an opportunity for a concluding discussion with question 9, where you might want to consider all the different aspects that you've discussed today.

I think, to clarify, question 5 and the voting question 6 here go together. And so although we're asking you about study 3 in isolation with question 5, what we're really trying to do is get you to consider what results were presented for study 3; and then, in the context of what you each have individually concluded about study 1 and study 2, think about what study 3 does to your perception of the aggregate of those two studies.

That's what we're trying to allow this question to build to. I think it's rather obvious

why we're interested in it. It's a failed study in terms of its primary outcome, and it would argue against an interpretation of the first two trials as being suggestive of efficacy on face. And we're trying to sort out what you all think about that.

DR. ALEXANDER: Thank you.

Dr. Zivin?

DR. ZIVIN: I'd like to get back to that question I tried asking you before, the sponsor, but clearly I didn't get it understood. What I would like to rephrase it as is, on the primary endpoint, is it 50 percent better, 20 percent better, 1 percent better?

DR. ALEXANDER: Can you clarify the referent? You say, is it -- and with what study are you referring to? If you could be more precise regarding the question or try rewording it.

DR. ZIVIN: With the primary endpoint and with reference to placebo.

DR. ALEXANDER: In what study?

DR. ZIVIN: Three.

DR. ALEXANDER: So the question is, in

study 3, what's the --

DR. ZIVIN: The magnitude of the difference.

DR. ALEXANDER: -- what's the relative magnitude of the difference?

DR. ZIVIN: Right.

DR. ALEXANDER: Dr. Temple?

DR. TEMPLE: Well, I'm still not clear what the question was. The difference in increase in walking distance -- the distance in walking distance was 10 meters out of something like 350. So is that what you're asking? That's what the nominal difference was.

DR. ZIVIN: Not the nominal difference. I want the relative difference.

DR. DUNN: There's a numerical difference of about 10 meters.

DR. TEMPLE: So you could say that's 10/300ths or something. Is that what -- that's about 3 percent. Right? Is that what you mean?

DR. FARKAS: We could show, perhaps --

DR. DUNN: Slide 12.

DR. FARKAS: -- slide 12. One thing that's

impressed us, too, is the similarity of where both arms are going. Maybe that's the question that you're getting at, that the drug-treated arm decreased 40 meters, if I'm reading that right, and the -- sorry, I might again -- one went down 40 meters, the other went down 50 meters, if that's the question.

DR. ZIVIN: Well, no. I'm still trying to get at is -- so you're saying it's 52 divided by 42.

DR. FARKAS: No. No, minus.

DR. TEMPLE: Minus for the 10, to get the 10-meter difference.

DR. TEMPLE: You could describe that as saying it went down 20 percent less, I guess. Right? That would all be determined by what the change over time was, which could vary from one population to another.

DR. ALEXANDER: Dr. Zivin, do the numbers there on the graph allow you to do the math that you want to do?

DR. ZIVIN: I'm sorry. I can't hear you.

DR. ALEXANDER: Do the numbers that are presented here allow for you to answer the question that you posed?

DR. ZIVIN: Yes.

DR. ALEXANDER: Thank you.

Dr. Unger?

DR. UNGER: Yes. I'm glad you got your answer. But if one went down by 1 meter and the other went down by 2 meters, I guess you'd say there's a 100 percent difference. But many would interpret that as no difference.

So I think if you're trying to put the change in perspective, 10 meters, you have to consider where people started, which is also in the slide, which is 348 meters or 337 meters. That's all I wanted to say.

DR. ALEXANDER: Thank you for that comment.

Dr. Farkas?

DR. FARKAS: I think, too, one of the things that -- I'm directing this to the public now -- there's a question of, if the 10-meter difference occurred due to drug or only by chance.

So we want to make it perfectly clear that at the FDA, we wouldn't object to a 10-meter benefit if that was real. But when we look at the p value and see the .42, that means that if you looked at the scatter of all the patients, which was quite wide, that you would get a result -- even if there's no drug involved, you would get a result like this fairly often, entirely by chance.

So just to make sure that people understand that we're not talking about clinical meaning. We're talking about differentiating things that occurred entirely by chance versus drug effect.

DR. ALEXANDER: Thank you.

Dr. Bagiella?

DR. BAGIELLA: I have a question for the sponsors and then a consideration after that. This study was powered to detect what?

DR. FUCHS: The study was powered to detect a 30-meter difference with the assumption of a 55-meter standard deviation of the change from baseline.

DR. BAGIELLA: Thank you. And a

consideration that I would like to make is the big difference between the study 3 compared to the study 1 and study 2, where in those two studies, there was an increase, actually, in the 6-minute walk from baseline through week 24 or week 48. So the difference between the placebo and the drug was an improvement, somehow, of the treatment group compared to the non-treatment group.

In this study, the difference is a less of a worsening. So I think that that is an important thing to keep in mind when we consider this. Both groups go down, and the treatment group goes down less than -- for 10 meters -- than the other one.

DR. ALEXANDER: Thank you.

Dr. Kesselheim and then Dr. Foley after that.

DR. KESSELHEIM: So in the spirit of stimulating some discussion, I find this to be a larger study that was more convincing in terms of the effect of the drug.

Although this wasn't listed as a discussion item, I was not as convinced by the post hoc

subgroup analysis except as a hypothesis-generating exercise. So I put more weight on this study and its design and endpoints than I did on the two smaller phase 2 studies.

DR. ALEXANDER: Thank you.

Dr. Foley?

DR. FOLEY: Just a question about the ages. We have it here for the phase 3, the ages of the placebo and the treated arms. But how about in the study 2? What were the ages of the patients?

DR. ALEXANDER: I'm sorry. Can you repeat the question?

DR. FOLEY: I'm asking about the ages of the patients in study 2 -- sorry -- yes. We have study 3's ages here, but we don't have the ages for study 2. Do we know what their ages were?

DR. ALEXANDER: So we'd like to understand the differences in the ages between patients in study 2 and study 3. And this is in the context of trying to interpret the null findings for study 3?

DR. FOLEY: Exactly. Thank you.

DR. FARKAS: I'm sure the sponsor has it,

but slide 2 from the FDA has the averages. At the bottom.

DR. ALEXANDER: Does someone want to just briefly walk us through this or highlight -- it looks as if the ages in study 2 is 7.8 years, with a range of 5 to 13, and in study 3 is 8.2 years, with a range from 5 to 16. And I think that we heard previously that study 3 was not only larger but, as Dr. Kesselheim pointed out, more heterogeneous and older, and then once again included more patients with greater disability.

I guess one of the points that I would make is in trying to understand this is in thinking about how the product, if approved, would likely be applied in the real world. And I would return to the question earlier that Dr. Kesselheim posed as to what the label would be.

I guess I understand a rationale for a broad -- I understand some of the arguments in favor of a broad label. On the other hand, here with the largest and most heterogeneous and arguably real world study, we don't see any

statistically significant effect on the primary outcome.

Yes, Dr. Farkas?

DR. FARKAS: I think that I'd have to echo what Dr. Dunn said earlier about it's difficult to talk about labeling in detail for this drug. But we recently, working with Parent Project Muscular Dystrophy, released a guidance where we said -- and I can't quite quote the each words -- where we said, we would do whatever was scientifically supportable to make as broad an indication as we could. I think that means a lot towards maybe some of the concerns that people have.

DR. ALEXANDER: Dr. Gonzales?

DR. GONZALES: I'm just going to piggyback on your comments from the chair. I know it's called an efficacy study, but for me this is more of an effectiveness study, exactly as you pointed out. This is what we're looking at in the real world with different centers not involved in the first two studies.

So for me, this was a lot more convincing

about what we might see if the drug is actually approved. And the findings are not nearly as robust when the inclusion criteria are broadened, or maybe the drug doesn't have the effect that we thought it had.

DR. ALEXANDER: Thank you. I think in the interest of time, if it's okay, I'll suggest that we move on. But let me in this case summarize before rather than after we vote. We can discuss the totality of evidence from all of the clinical development, from the full clinical development program, during the concluding discussion.

The numerical difference was about 10 meters of an increase in walking distance out of something like 350 meters at baseline. One, the treatment arm decreased 42 meters; the other, the placebo decreased 52 meters. So there was a contrast where in this study, both arms declined, whereas in a previous study, I think that there were increases instead.

There was a point made that one can't look at the relative changes alone. One could imagine a

difference between a 1- and a 2-meter decline, which would represent 100 percent change, yet obviously not be clinically significant, or at least many would argue that it might not be clinically significant.

The FDA would not object to a potential effect of 10 meters if it was real, but in this case there was no statistically significant difference, and one could see this magnitude of difference commonly by chance alone.

Study 3 was powered to detect a 30-meter difference with an assumption of a 55-meter standard deviation with respect to change from baseline. The difference between the placebo and the drug was improvement -- I'm sorry.

Study 3 was a larger study, more convincing in terms of the effect of the drug. Some were not as convinced by the post hoc subgroup analyses except as hypothesis-generating exercises. Some felt that more weight should be applied to this study and its design, given its design, than the smaller phase 2 studies.

There was a comment that this was closer to an effectiveness study than an efficacy study, closer to what might be more likely to be seen in the real world, although the findings are not as robust or indeed statistically significant.

A comment regarding labeling, that it's difficult to discuss labeling for this product and perhaps premature, but the FDA has released guidance, and the FDA has said they would do we have is scientifically supportable to make the product as widely available as possible, or something to that effect.

So next, we'll move to the question 6, which is, what is the impact of study 3 results -- I'm sorry. Dr. Farkas?

DR. FARKAS: Yes. I think that I had said something that you had just repeated about the size of the effect and what we would do about approval, and perhaps speaking faster than my brain was working, which was pointed out to me.

Of course, there are problems with -- again, mouth speaking faster than the brain. But I think

I oversimplified that a little bit. That would be one thing. There are certainly questions about risk/benefit and I think, too, about where that change might be going in the future.

I guess I would leave it at that and add that if anybody else next to me wanted to add something, I would certainly invite them.

DR. DUNN: Sure. I think the clarifications Dr. Farkas is making just have to do with the nature of understanding any given outcome measure and recognizing that we are going to take it into context. And I think a good description of our approach to this for Duchenne is contained in our guidance.

Six-minute walk test is clearly an example of a measure, which we work with sponsors on and we find to be potentially interpretable. But we obviously have to take it into full context. And any clinically meaningful difference on an acceptable outcome measure is something that we would certainly find acceptable. But that's the nature of the development and review process that

we need to ascertain.

I think what Dr. Farkas is suggesting is there's not a hard cutoff. There's not a certain number that necessarily goes along with that at any moment, but that we're prepared to accept any clinically meaningful difference.

DR. ALEXANDER: Sure. Thank you for that clarification.

We'll move to question 6, which is, what is the impact of the study 3 results on the persuasiveness of findings from studies 1 and 2? Does it strengthen the persuasiveness of the findings from the studies 1 and 2? Does it weaken the persuasiveness of the findings from the studies 1 and 2? Or does it have no effect on the persuasiveness of the findings from the studies 1 and 2?

So this question is now -- or will be open for voting in a minute.

(Pause.)

DR. ALEXANDER: Can you enter your votes a second time? I'm not sure that the votes went

through.

(Vote taken.)

DR. BAUTISTA: The vote is now closed. I will now read the vote into the record. Zero panel members voted for A; 15 panel members voted for B; 2 panel members voted for C.

DR. ALEXANDER: Thank you. So we'll begin with Dr. Estrella. If you could please report your name and your vote and your brief rationale.

DR. ESTRELLA: My name is Michelle Estrella. My vote was for B, weaken. My two main reasons were the overall null findings for the more heterogeneous, larger population. And even when looking at the more narrowed population in the middle 50 percent in which the patient study population was narrowed to be to be more comparable to studies 1 and 2, there was really no signal to support efficacy. And the effect size was quite small at about a delta 5, and no statistical significance.

DR. FOLEY: Reghan Foley. I voted as well for B, weakens. The results were not significant

and really different than both studies 1 and 2. And it does reflect more accurately the general population with a wider age range, so I think it's important.

DR. NUCKOLLS: Glen Nuckolls. I voted B, for the same reason as Dr. Estrella.

DR. LEVINE: Rodney Levine. I voted B, that it weakens because this is a phase 3, well-designed trial that failed to meet its endpoint, primary endpoint.

MS. GUNVALSON: I'm Cheri Gunvalson. I'm a nurse. I didn't know I'd need statistics to do this, and I maybe didn't vote right. But what I believe is if a parent looked at this, with this disease and with the age group of 5- to 16-year-olds, they would take a possible 10-meter advantage. And maybe I'm not figuring it out right, but in face of a lethal diagnosis, it's better than what we've got.

DR. DUNN: Dr. Alexander, pardon me.

Ms. Gunvalson, could I just ask you to clarify what you meant by "maybe I didn't vote

right"? I understand the comments you made about how you would interpret the result.

MS. GUNVALSON: Well, as a parent, I would take this 10-meter differential possibility. So by voting C, I hope that vote followed what I -- if the vote -- I told you what I felt. So if the way I voted didn't enforce that, tell me.

DR. ALEXANDER: Yes. The question was really about whether or not you felt that the results from study 3 changed your feelings about how convincing the results were or how persuasive the results were from studies 1 and 2.

So it really was focusing on how you put together those three studies. But I think your comments are very helpful, and I think we can just take them as they are.

MS. GUNVALSON: So you can just take away my vote. My comments is what I want.

DR. DUNN: Yes, ma'am. Thank you. I understand your comments. Thank you.

DR. HOFFMANN: Richard Hoffmann. I voted B, for the same reasons the other people cited. But I

do think that there should be given considerable consideration to the post hoc analyses by the sponsor.

MR. CASSIDY: Chris Cassidy. I voted that it neither strengthened nor weakened. I do appreciate the fact that BioMarin did broaden the criteria for inclusion of subjects, but I do agree with their post hoc analysis that in selecting a more heterogeneous group of older patients and more functionally impaired, it did skew the data.

So I don't think it was as convincing as it could have been, again just because it's skewed toward -- well, the inclusion of older patients, the more functionally impaired.

DR. GREEN: Mark Green. I voted B. With a high placebo response and a low therapeutic gain at every single time point, that drove my vote.

DR. ONYIKE: Chiadu Onyike. I voted B as well. I don't see a meaningful difference. And furthermore, phase 3 is supposed to be, in my view, anyway, confirmatory of the phase 2 studies, and the phase 2 results seem unstable, I suppose is the

best way to put it.

So in light of the more powered study, stronger design, and the findings we have here, one has to reevaluate the first two.

DR. GONZALES: Nicole Gonzales. I also voted for B. I'd like to echo Dr. Onyike's comments. In my opinion, study 1 appeared promising, study 2 less so. And as we gathered more information, including study 3, it seems like the treatment effect is actually more realistic now that we're seeing in study 3.

DR. ALEXANDER: Caleb Alexander. I voted B. It couldn't help but diminish my conviction about the findings in studies 1 and 2 and a number of post hoc analyses or potential explanations such as the more advanced disease, or inadequate treatment duration, or the various expertise of different centers in different countries, or a lack of a loading dose.

When seeing additional analyses that were done to explore whether those were likely to account for the findings, I wasn't convinced. So

it did decrease my belief about the persuasiveness of the first two studies.

DR. OVBIAGELE: Bruce Ovbiagele. I voted B as well, for largely all the reasons that have already been articulated by the other B voters.

DR. ZIVIN: Justin Zivin. When I was 8 years old, I was introduced to a neighbor who was in a wheelchair. He was 12. In his bedroom was medical equipment. In the dining room, there was exercise equipment. I would go and see him regularly.

We moved two years later, and he never told me that his disease was progressive. They may have told me what his disease was, but it wouldn't have meant anything to me.

I never forgot him. When I was a neurology resident, I read about Duchenne muscular dystrophy, and to me it was not just a textbook. Furthermore, in my own family, I grew up with a family member who has a debilitating neurological disease. And I saw growing up how disruptive that can be to families.

When I received the packet of information from the FDA, I first looked at the sponsor's material, and I thought, this is the most interesting idea I've seen in years. Then I read the FDA materials, and it was clear that this wasn't going to get approved at this point.

It gives me no pleasure whatever to vote B. This just needs more work.

DR. ALEXANDER: Thank you.

Dr. Bagiella?

DR. BAGIELLA: I voted B because -- so this was really the pivotal study for this drug. And although there was a signal in phase 1 and phase 2, the phase 3 study really failed to find a difference between the placebo and the drug.

What particularly drove my vote is that it seems like both groups degenerated over time, pretty much at the same time rate. And so the drug in any way helped to stop or improve the disease.

DR. MIELKE: Michelle Mielke. I also voted B, weaken, for a lot of the same reasons that were said. The first two studies were promising. The

third study was really the pivotal one that was well-powered to assess an effect.

It's possible that for particular individuals with certain characteristics, or if there was loading dose or something, that would be helpful down the road. So it doesn't mean that it's definitely not going to work or it hasn't worked for some people. But the overall results, I think, weaken the interpretation.

DR. KESSELHEIM: Aaron Kesselheim. I also voted B, and I would echo what Dr. Mielke just said. I think that it is possible that there are certain people in this trial who the drug possibly affected, and I'm hopeful that additional work can be done to identify those people in a prospective way.

But the trial as it was designed and as the results came out overall weakened my view of any signal that arise from the other two smaller studies.

DR. ROMITTI: Paul Romitti. I voted B as well. But I will say that I really felt I could

have cast two votes here. I feel the question is really two questions. I feel we're comparing apples and oranges. Study 1 had a loading dose. Studies 2 and 3 don't have loading doses. It's been mentioned by Dr. Alexander and Dr. Mielke.

So if I would say that it doesn't affect my interpretation of study 1, it does affect my interpretation of study 2 because these both were without loading doses, and it diminishes my interpretation of study 2.

I recognize this is a phase 3 trial. It's well powered. It's more real-world experience. And I asked before lunch, and just my curiosity is, what will a loading dose do to a more heterogeneous population of patients? And that can't be answered here.

DR. ALEXANDER: Thank you very much.

We'll move to question number 7. Drisapersen was designed to increase production of dystrophin. Discuss the evidence presented about dystrophin production, including the following:

Similar number of patients with skipped band

of mRNA detected by PCR in the placebo and drisapersen group;

B, similar number of patients with dystrophin increased from baseline in the placebo group and drisapersen group on immunofluorescence testing; and

C, lack of notable increase in dystrophin with drisapersen treatment on western blot analyses, pre-treatment levels less than 1 percent and post-treatment levels less than 1 percent.

Dr. Farkas?

DR. FARKAS: There was a clarifying slide that we should show. This didn't mention the immunofluorescence results, and I think that's where a number that Dr. Hoffmann saw came from before. I think that's backup slide 17.

So the data's a little bit complicated. And I think the point that we wanted to get across is first, Dr. Rao and Dr. Tandon, is the movement of all these points around zero, that isn't representing 10 percent of normal dystrophin expression.

That's representing the change, and the change from levels that are just slightly above zero, so something like a third of 1 percent of normal. So there's almost no movement at all, is one thing.

Then the other thing to look at here is that study 117 was -- I think that's where this something like a 4 percent number came from. And again, that 4 percent is not movement from zero percent to 4 percent of normal. It's movement from zero percent to 4 percent more than zero, almost zero percent. It's any movement on a very low number.

Then for 876, what to us is quite concerning is the results favored placebo. So there's this very small change, but the result favored placebo. So that to us was conflicting results around a very tiny potential movement.

DR. ALEXANDER: Dr. Green?

DR. GREEN: Well, if the study were very positive, you'd just have to conclude it's the wrong biomarker. Given the data we have, it's hard

to know really what to make of any of these levels.

DR. FARKAS: Right. I think maybe, if I could speak a little bit more, we go by empirical evidence, and we go by empirical biomarker evidence, too. And so we very much value the contribution of biomarkers to the clinical data and try to use them together.

DR. ALEXANDER: Yes. I have to say I'm puzzled on this one because I may have said this before, and I understand that there's agreement that this is not an appropriate biomarker. But on the other hand, you have a disease that's characterized by, if I understand it correctly, abnormal production of this protein, and you have a product whose mechanism of action is to produce an exon skip to allow for increased production of the truncated protein. And you have people that have a different form of the disorder that don't have the same degree of disability, and they have levels of 50 to 100 percent of the protein.

I just don't understand. I don't understand why there's not more production of this if this is

the mechanism of action. So I guess what I'm trying to figure out is, does the sponsor think or do we think that, actually, dystrophin is increased but we're just not measuring it?

One of the responses was that we're just assessing this in the tibialis or something. So is the thought that it's increased in the quads but not in the muscle where it's biopsied, or is the thought that it's not actually increased?

I don't understand what the mechanism of action of the drug is. If it's not increasing dystrophin, it sounds like it's an unknown mechanism of action. Maybe I'm missing something. But those are my two cents.

Dr. Mielke?

DR. MIELKE: I had many of the same questions because biologically you would expect an increase. So I go back to a point or at least something that I took from the sponsor about the FDA workshop in March of 2015, of dystrophin as a biomarker in Duchenne.

Can we adequately measure this biomarker?

So the current dystrophin is going to be shorter. Do the assays that are being used still try to measure the longer form? Are the measurements adequate for measuring what we're trying to measure?

DR. RAO: Ashutosh Rao, OBP.

DR. ALEXANDER: Dr. Rao?

DR. RAO: It's our understanding that --

DR. ALEXANDER: Can you introduce yourself, please?

DR. RAO: Ashutosh Rao, Office of Biotechnology Products.

It's our understanding that even though there's still room for improvement in dystrophin methodologies and it's still evolving in terms of how much and newer methodologies that can have precision at very low levels, the methods that the applicant submitted to us are capable of telling you if there is a real increase.

Their use of multiple methods, just for the sake of argument, orthogonal methods, where you have different assays to measure the same endpoint,

does add confidence that even though there may be room for improvement in individual methods by a combination of methods. Yes, you are able to tell where the protein is and an estimate of how much it is. There is of course room for improvement. But yes, the methods are capable.

DR. ALEXANDER: I wondered if the sponsor wanted to, either now or after the next question, just address the question of whether they believe that there is increased dystrophin production, but that it's just not being assessed; or that in fact this drug is acting to produce the efficacy that we have seen without increased dystrophin production. And if the latter, what is it that you believe is the mechanism of action of the product?

DR. FUCHS: We believe that the mechanism of effect is via increasing dystrophin. I think, if I could have slide -- by increasing dystrophin -- I think one of the biggest challenges in this field is we're imagining that this is like a secreted protein, and it's simple to measure, and it does exactly one thing.

This is an incredibly complex protein that has multiple functions in multiple tissues. And we use immunofluorescence to detect its presence from a quantitation point of view, but that's not necessarily the same thing as measuring its function.

In our integrated pharmacology model, what we showed you was that when you drive drisapersen into the body, immunofluorescent expression of dystrophin increases the challenge of study to interpretation, as there are no baseline samples. So you don't know what to compare it to.

Dr. Farkas is right. We're talking about relatively small increases, but we're also looking in the best-preserved muscle, tibialis anterior, where A, drug delivery is relatively low, and preexisting damage is relatively low. So you may not expect to see relatively high effects.

Across all three of our studies, we believe that we see an improvement in -- if I could have slide 2 up -- the relationship between tissue levels -- I'm sorry. I meant slide 3 up. We see a

relationship between increasing tissue concentrations of drisapersen and increasing walk across all three of our studies.

Then if I could have the previous slide up, across three studies we see evidence of increasing dystrophin across the three studies. The team is looking for the slide that we just had up with the three panels of dystrophin. Yes. If I could have slide 3 up. Apologies, it got obscured here. If I could have slide 3 up.

So in study 1, we see an increase from Pre-treatment baseline. In study 2, we see an increase. It takes a while in the absence of the loading dose. Because of the long persistence of dystrophin levels and the long persistence of drisapersen in the tissues, you see an effect even when the study drug is withdrawn.

Then in the phase 3 study, in the study 3, you do see a trend towards increased dystrophin, acknowledging there are no pre-treatment samples, so you can't really be sure what you're comparing to.

This pattern, which consistently repeats itself and is associated -- if I could have slide 2 up -- across the board with the clinical pharmacology, exon skipping dystrophin changes, and clinical benefit, is a consistent pattern.

I think that -- slide down -- if I could just summarize by saying, there are signals here. In the rare disease world, it can be very difficult to comprehensively demonstrate benefits in internal consistency across primary and secondary endpoints at a statistical level and across studies, especially when the velocity of change in the population is changing so dramatically.

DR. ALEXANDER: Thank you. So if I understood correctly or heard correctly, the FDA has suggested that the multiple assays, they believe, are sensitive and able to accurately identify dystrophin levels, and if I understand, that the sponsor has made the point that you do believe that the mechanism of action is increased dystrophin, but we see levels that remain less than 1 percent of normal.

Dr. Levine, do you want to comment?

DR. LEVINE: Well, my research and my research group has decades of experience in quantitating specific proteins, and in particular, proteins that have subtle modifications in them.

So I could give you my own assessment of the three different techniques, but since this is tied to what we're going to vote on in 8, I'm going to suggest that it is irrelevant. It's the clinical results that matter.

DR. ALEXANDER: So you believe that the levels of dystrophin are irrelevant to understanding this product or its mechanism of action?

DR. LEVINE: No. I didn't say that. In terms of assessing whether drisapersen is effective, it's irrelevant. The results are very important in understanding whether, if it's considered efficacious, it's acting by the proposed mechanism or not.

DR. ALEXANDER: Thank you.

Dr. Bagiella?

DR. BAGIELLA: Are there preclinical studies or in vitro studies that show that the drug can actually increase the level of dystrophin?

DR. FUCHS: We have done a lot of work preclinically to show that you can increase dystrophin, and we have done imaging studies in humans. They're included in the package. And there is a reduction of fat and fiber infiltration, but it's not the same thing as measuring dystrophin directly by imaging. I'll leave it at that and see if you want to dive in a particular place.

DR. RAO: If I could add on to the response that I gave earlier, and I'm going to try to address both questions -- this is Ashutosh Rao, Office of Biotechnology Products. If I could have slide 36 from the FDA deck, please.

Our understanding of the complications of dystrophin and its measurement, like I said, still evolving. Room for improvement. But there is a definite need for other factors to come into the measurement to aid the confidence of any type of data interpretation. These are some of the factors

that, in general, the field struggles with.

In the case of dystrophin, you have heterogeneity in the muscle, heterogeneity in the dystrophin protein, truncated forms, isoforms, that do complicate the measurement. The inflammatory environment in Duchenne and the contribution of any inflammatory response to the newly expressed dystrophin is also a complicating factor.

The stage of the muscle fiber and the fibrosis and the degeneration that occurs, and whether you have actually caught it at a time point where it's too late even if you were to re-express dystrophin, is a question that we don't know the answer to.

So on this slide we've summarized some of the complications that are absolutely present that do complicate the interpretation. Having said that, yes, there is data from preclinical models that can show an increase in dystrophin. The sponsor's own data does have a few patients that did show an increase.

So the 4 percent that was used as an assay

cutoff for immunofluorescence and the 30 percent that was used for western blot, there were a few examples where there was an increase, but not necessarily between placebo and treatment or consistently between the studies.

DR. ALEXANDER: Thank you.

Dr. Romitti?

DR. ROMITTI: I had a question. I'm going to switch gear. I see Dr. Mielke's hand up. I was going to ask about the quality of the measurement. Did you want to follow up with the discussion first on the values?

DR. MIELKE: My understanding, which Dr. Alexander mentioned, the quality you can measure but you can't measure the functionality. So we still don't have the assays that would measure that. That may be more important than the actual quality. Correct?

DR. FUCHS: Well, it's our belief that the best way to measure the function of the protein is to measure how well the muscles can perform. In study 1 we demonstrated a 35-meter improvement,

study 2 a 27-meter improvement, in study 3, with a very broad population, a 10-meter improvement. That's the best way that we have today to measure the function.

Unfortunately, there's no comprehensive way to integrate the secondary endpoints. You heard so much about how patients feel different from each other, and that methodology just doesn't exist today.

DR. ALEXANDER: Those improvements in the second and third case were of borderline or nonstatistical significance. Is that right?

DR. FUCHS: I would agree with Dr. Temple's comment that p-values can make you crazy if you stare at them too much. In the rare disease world, it's very difficult to get. And we look at the total body of evidence, integrating across our studies.

DR. MIELKE: Sorry. Can I follow up on that? But there's some question about the selection because there are a lot of people that didn't have the dystrophin measures, and you didn't

have the muscle, and how representative are those that you do have it on. But was there any evidence that those that did have higher dystrophin levels performed any better?

DR. FUCHS: We are unable -- and Dr. McDonald mentioned it's true in the natural history setting, and Dr. Rao mentioned it in the natural history setting, I think. I don't want to put words in Dr. Rao's mouth. So Dr. McDonald mentioned it.

There isn't comprehensive evidence at the individual level that a change in dystrophin is correlated with a change in walk. If I could have slide 1 up.

Just amalgamating the evidence from study 1, if we look at percent change in dystrophin -- again, this is a relative percent change; Dr. Farkas is going to remind us again about that -- on the horizontal axis, to the favorable to the right and to the vertical is the improvement in 6-minute walk distance, in grey is the placebo group where you don't see much change

in dystrophin and you do see some deterioration in the walk, and in the pink is in the population you see an improvement in dystrophin and an improvement in walk.

The values here are not identical to the full cohort simply because these are measures in which we have both the dystrophin level and measures of the change in the clinical outcome variables. We make no effort to impute or censor. If I could have the slide down, then.

The summary of this is that this is why we keep coming back to we believe the drug works by exon skipping and not through some other mechanism. Tibialis anterior, very difficult. We're talking about wanting to see something from almost the moon, that's how far away we are from the dystrophin apparatus.

But there is some signal there. And really, that evidence together with the clinical evidence across the trials is the primary basis for evaluation of the benefit, together, I think, with what we're heard from the audience in terms of

heterogeneity of effect.

DR. ALEXANDER: Dr. Bastings? I'm sorry. Dr. Dunn, did you want to comment?

DR. DUNN: I wanted to take a moment, if there's a pause in the conversation, to come back to the point that you made.

I don't want there to be any misunderstandings about this question as suggesting that a biomarker result of uncertain but plausible significance would trump impressive clinical results, or clear clinical results, might be a better term. That's not the intent of this question.

But when dealing with some inconsistencies in clinical data, whereas we've been trying to sort out how resilient they are to probing their strength, I think that Dr. Alexander's initial commentary about how he described the dystrophin issues with regard to the mechanism of action of the drug, what it's expected to do, and what we see, this is another way to contextualize these clinical findings that we're trying to wrestle

with.

So just as a way to let the committee know what we're trying to get at here, it's just another line of reasoning to help us try to sort things out. And we note that there was really no significant increase where we could measure it.

Further, if we're looking at it in a regional way, as might be suggested, that we're just not detecting it in a good spot, we also see very small differences, if any, between the placebo and the treated groups with some other assays.

So just for a little contextualization there, we're not suggesting that this would trump clearly interpretable clinical results. That's not what this question is getting at.

DR. ALEXANDER: Dr. Nuckolls?

DR. NUCKOLLS: Nuckolls, yes. Can the sponsor remind us what percentage of biopsies were determined to be unusable, and what is the criteria for determining they're unusable?

DR. VAN DEUTEKOM: My name is Judith Van Deutekom, head of drug discovery, BioMarin, Leiden.

To detect an increase in dystrophin pre-versus post-treatment, you need good quality biopsies. And in study 2 but also in study 3, there were issues with that. So study 2, 33 percent of the biopsies were not -- so it's either pre or post. You need to have both in good quality to do the comparison.

So for 33 percent of the patients in study 2, it was not possible to make this assessment. And in study 3, it was even 48 percent.

DR. ALEXANDER: Thank you.

DR. NUCKOLLS: Is there criteria for determining that it's not usable?

DR. VAN DEUTEKOM: Numbers of fibers. So the immunofluorescence analysis looks at the dystrophin intensity over the entire membrane in the entire fiber population. And so at least 400 fibers need to be countable. So if the quality of biopsy is not good enough to do so, either pre or post, then we did not do the assessment.

DR. ALEXANDER: Thank you.

Maybe just one or two more questions. Dr. Onyike?

DR. ONYIKE: I wonder if there are any studies of dystrophin infusions, either in laboratory animals, for example, and whether such infusions resulted in measurable improvements.

DR. FUCHS: I would dare say that probably Dr. Van Deutekom knows more about dystrophin and pharmacology than most people. And it's such a large protein, and you have to be delivered to the membrane, and it's got these signaling properties. And we're not aware of any efforts to replace dystrophin exogenously.

DR. RAO: If I could just clarify on that. Ashutosh Rao, Office of Biotechnology Products. There have been gene therapy efforts, for example, in the past. And the Center for Biologics is responsible for that regulation.

Dystrophin protein expression as a purified protein to put back is very difficult to do. It's a huge protein. It's 427 kilodaltons. So efforts to so far actually make a protein even for

experimental systems and for biological assays such as this have not been successful. So that second step has not been taken to actually put it back in people, to the best of my knowledge.

DR. ALEXANDER: Thank you.

Dr. Farkas?

DR. FARKAS: Well, I've read the nonclinical data and what's published, and I don't profess to be an expert in all of it. But it did seem all to line up as you'd expect.

I don't know if I'd get into more detail than that, that there was what looked like support for the mechanism in the nonclinical studies, that there was detection of dystrophin and a change in the condition of the animals.

DR. ALEXANDER: Thank you. I think, if it's okay, we'll move to the voting section of this question after I summarize the discussion. But maybe one brief question from Dr. Bagiella, and then also you'll have an opportunity to provide more comments as you explain the rationale for your vote.

So a final question, Dr. Bagiella?

DR. BAGIELLA: Yes. My question is about the question, actually. When you ask what is the impact of the dystrophin results on the interpretation of the clinical results, and then we have strengthen, weaken, or no effect, are you looking for us to determine whether or not the dystrophin results corroborate the clinical results, yes or no, or has no effect, or whether they suggest something else?

DR. DUNN: Sure. I think, to be as succinct as possible, whatever credibility you assign to the clinical data, we're wondering what the dystrophin results do to your assessment of that credibility.

DR. ALEXANDER: Thank you. I'd like to try to summarize briefly what I've heard.

There was a question about immunofluorescence results, and the point was made that movement of all the study points around zero is representing change from levels that are just slightly above zero, and so there's almost no change in absolute dystrophin expression. So

4 percent in study 117 is not from zero to 4 percent of normal; it remains less than 1 percent.

Study 876, I believe the dystrophin results favored placebo. There was a point that the FDA goes by empirical evidence, including empirical biomarker evidence.

There was a question raised regarding that there's an unclear mechanism of action, and what is the effect of this, the study drug, if not processed dystrophin production. The sponsor clarified that they do believe that the mechanism of action is by increasing dystrophin, so they suggested that it is increased but that it's difficult to assess.

The FDA pointed out that there are fairly precise ways to assess it. But they also highlighted a number of complexities in that assessment that I'll mention in a minute.

There was a point made regarding that the relative increases in dystrophin are important to understand with respect to mechanisms of action of

the drug, but not an understanding of the clinical outcomes or the endpoints that are of interest to patients and families and others.

In vitro studies indicate that one can increase dystrophin, including imaging studies in humans, but this is different than measuring it directly, as in these studies.

Some of the complexities of measurement are the heterogeneity of samples and the variety of other factors that complicate measurements. In general, bioassays need to be appropriately validated prior to critical application. The combined use of several different bioassays may allow for reasonable estimates of its location and amount.

There was a question whether we have assays that measure the functionality of the protein, and the point was made that the best way to do this is how well the muscles perform, which is what the sponsor has assessed in the studies provided.

A point was made that p-values can make you crazy and that one looks at the totality of the

body of evidence across studies.

There was a question as to whether there was evidence of higher dystrophin leading to better performance, and it was stated that there's not comprehensive evidence that changes in dystrophin at an individual level are correlated with a change in walk, although once again reminding you that these are changes from an arguably infinitesimally smaller, very, very small amount to still a very, very small amount, less than 1 percent.

The FDA made a point that no biomarker of uncertain significance would trump a clinical result of clear and consistent difference.

There was a question regarding what percentage of biopsies were unusable and what the criteria were for determining this, and we heard those statistics.

Last, there was a question about the study of dystrophin in fusions, and it sounds as if this is a large protein and putting it back in the body is exceedingly difficult, even to make it, let alone to reinfuse it. And thus, although there

have been studies of gene therapy with dystrophin, there's been no substantial effort to investigate reinfusing it.

So with that, I think we'll move to the voting question. The question is, what is the impact of the dystrophin results on the interpretation of the clinical results? Does it A, strengthen the clinical results, does it B, weaken the interpretation of the clinical results, or C, does it have no effect on the interpretation of the clinical results?

So are there any questions regarding the technical wording of question 8? Yes, Dr. Onyike?

DR. ONYIKE: Yes. I'm just wondering, when we ask if it strengthens or weakens an interpretation, whose interpretation are we referring to?

(Laughter.)

DR. DUNN: I'm sorry. I thought I addressed that previously. But yours. Whatever credibility you assign to the clinical results.

DR. ONYIKE: In other words, if one assigns

zero credibility, then you would say strengthen, perhaps?

DR. DUNN: I suppose you could, yes.

DR. ONYIKE: Will that create some confusion in your ABC system?

DR. DUNN: We'll listen carefully to your explanations.

DR. ALEXANDER: Thank you.

So if we can have -- yes, another point of clarification?

DR. ROMITTI: Yes. Just a clarification. I want to go back to Dr. Levine's comments on the importance of does this really have an impact on the question? But the mechanism of action is very important for the drug.

So I need clarity from the FDA on how important knowing the mechanistic action of the drug is to this process, not just our interpretation of what it does to the clinical data.

DR. TEMPLE: Well, that's a difficult question, for a number of reasons. There's lots of

drugs that work in ways we don't understand. If they work, we approve them, even if we don't know the mechanism.

What's unusual here is that the mechanism is strikingly targeted. I mean, as near as one can tell, it only does one thing. And if it doesn't do that thing, which is the putative mechanism, it certainly would make you wonder.

But what we're asking you really is how you weigh all that stuff. But in this case, I guess if you were really convinced that it had nothing to do with dystrophin, you'd say, well, how would it work at all? On the other hand, if the evidence were very, very strong, just because you didn't understand how it worked, you might swallow it anyway. It's not a simple question.

But in this case, you're right. The implication of your question is right. That is, there isn't any obscure mechanism that's plausible here. The whole drug is designed to do a particular thing. And if you can't show that it does that, what's the effect of that? And that's

what we're asking.

DR. ALEXANDER: Thank you. So with that, I think we'll move to the voting, unless there's a further question about the technical wording of the question.

Yes, Ms. Gunvalson?

MS. GUNVALSON: I have a question. If there's no body of evidence that states increased dystrophin affects the walk -- right? Was that what you said? And I know boys who have zero dystrophin who are in better shape than boys that have some dystrophin. I mean, it's a puzzle.

So it's difficult to know how to answer this question, if it's mechanism you're looking at or functionality. I just was wondering if you had any more --

DR. ALEXANDER: Yes. First, to be clear for the record, I was not stating the truth but simply stating what I heard when I mentioned that there may have been limited evidence to support an association between changes in dystrophin levels and changes in function.

But I think, if I can try to answer your question, I think that if you believe that dystrophin is not a credible marker or surrogate or signal for whether this product is working, then I think that that would be a C, no effect; that is, that seeing that dystrophin is or isn't high or low wouldn't change your belief about the clinical results that you've seen.

MS. GUNVALSON: But as Dr. Temple said, sometimes drugs have an effect and you don't know if it -- I don't know. Could this be increasing utrophin? Is that an effect? I don't know. I'm not the --

DR. ALEXANDER: We'll have an opportunity to discuss the rationale for our votes. And I think as is often the case, the qualitative feedback that we provide to the agency is as valuable as A, B, or C.

MS. GUNVALSON: Thank you.

DR. ALEXANDER: Thank you. So if we can have the vote, then.

(Vote taken.)

DR. ALEXANDER: I just wanted to let people know Dr. Hoffmann had to leave, so he is not participating in this vote.

DR. BAUTISTA: This is Phil Bautista, the DFO. The vote is now closed. I'd like to read it into the record. Zero members of the committee voted for A; 6 members of the committee voted for B; 10 members of the committee voted for C. There is one no-vote.

DR. ALEXANDER: Thank you.

Why don't we begin with Dr. Estrella. If you could read your name and vote into the record and a brief rationale.

DR. ESTRELLA: My name is Michelle Estrella. My vote was for C, no effect. And my vote was mainly based on the fact that I wasn't completely convinced that dystrophin levels were reliably reflective of the effect of the drug on clinical parameters.

DR. FOLEY: Reghan Foley, and I also voted C, no effect. My rationale was, I think that sometimes both the clinical result and the protein

expression are reliant on the efficacy of skipping in a particular patient.

So as we're seeing clinically, some patients do respond, and likewise, some biopsies do produce increased protein expression, albeit at a smaller quantity than hoped for. But I think it doesn't really affect -- in my mind, it was probably reflective of the individual variation in efficacy of skipping.

DR. NUCKOLLS: Glen Nuckolls. I voted B. I think that increased dystrophin above the noise level is a required signal for the function of this drug. I'm also quite troubled that so many boys had biopsies taken without useful data, and I really think that needs to be addressed in future trial design.

DR. LEVINE: Rodney Levine. I voted C, no effect. Actually, I think the measurements of dystrophin are quite consistent with the clinical results in the strongest study, the third one, which failed to find a clinical effect.

MS. GUNVALSON: Well, this is difficult. If

you're looking at the mechanism, that's why I voted B. It didn't meet the criteria. But I still have very mixed feelings about the role of dystrophin and the way it's quantified. And when you have clinics all over the world doing it and how they are done, and the staining of it, I just don't know how great the consistency of the staining and such is.

MR. CASSIDY: Christopher Cassidy. I voted B, weakens. This drug, as said, is very targeted, and its mechanism of action is to increase dystrophin. And I feel that there should be higher levels, but there isn't.

I'm also concerned about the number of muscle biopsies as well as Dr. Nuckolls. I'm concerned about the number of muscle biopsies taken, often to no avail. Thank you.

DR. GREEN: Mark Green. I voted C. I can't tell whether it's an active protein, an inactive protein, or whether it's heterogeneous throughout the body. And there's just too many factors that don't help me understand how it has to correlate

with clinical activity.

DR. ONYIKE: Chiadu Onyike. I voted C. The rationale -- well, let me say that the rationale going into the study as I perceive it is based on observations in Becker's muscle dystrophy.

What we're seeing are dystrophin levels that are perhaps two or three orders of magnitude lower than what the drug should be producing if indeed the inspiration is the observations both in dystrophin as well as in the clinical picture of the Becker's cases.

So I subscribe to what Dr. Levine has said now and earlier, when he said it probably doesn't really matter, given the results in phase 3. Most are sympathetic to what Dr. Nuckolls has mentioned.

DR. GONZALES: Nicole Gonzales. I voted for C, and I echo what Dr. Green commented.

DR. ALEXANDER: Caleb Alexander. I voted B. I'm just trying to figure out where it is. If there is the belief that the drug acts through increasing dystrophin and the sponsor believes that this is the case, I would have expected more

discernible increase following exposure to the study drug.

I guess I would hang my hat more on dystrophin than LDH and CK for some of the reasons I'm not sure we got into all of the details. But I think that it's certainly a more direct measure of the effect of the product, and we saw in some of the briefing materials some inclusion of LDH and CK as supportive evidence when in fact you could tell different -- through different mechanisms, one could hypothesize an increase or a decrease in those levels.

I thought dystrophin would be much more conclusive to see changes in its production and identification in the tissues of interest.

DR. OVBIAGELE: Bruce Ovbiagele. I voted C, no effect on the results of the interpretation of the clinical results. And like many people, I was trying to wrap my head around the question itself, so I actually had to write out the various scenarios.

Positive efficacy, clear efficacy, increased

dystrophin; no efficacy, increased dystrophin; positive efficacy, no increase in dystrophin; and then finally, no efficacy and no increase in dystrophin.

The latter is what I see or I think is the import of all the results that we've seen. If that's the case, then I don't think that results of dystrophin actually have any clear interpretation or effect on any clinical results because there was no efficacy.

The other big issue, of course, is that the assessment is very complex. So yet again, with a complex assessment or measurement method, I think it really doesn't have any discernible effect on the clinical results.

DR. ZIVIN: Justin Zivin. I agree with a lot of the things that people have been saying. In addition, I view it as a biomarker, and almost no biomarkers work.

DR. BAGIELLA: I voted B, mainly because, again, I counted in some way on the mechanism of action of this drug. And I think that even in face

of non-positive clinical results, if they had found the signal for the biomarker, they would have explained that something was moving.

In this way, it seems like nothing is really moving. So I don't think that this can in any way corroborate the results.

DR. MIELKE: Michelle Mielke. I voted C, no effect, primarily because I thought the results on dystrophin were inconclusive. There were several people that didn't have dystrophin measures. And as a biomarker, there's still, to me, not a good understanding between the levels and the effect on many of the functional measurements, and that much more understanding there is needed, particularly, if I can add, just going forward in further research to determine whether that might be an indicator of who may be most responsive.

DR. KESSELHEIM: Aaron Kesselheim. I voted B. As others have said, I had a tough time figuring out how it is that a drug that's supposed to work by increasing dystrophin levels and all the clinical measures that are measured in the clinical

studies -- a lot of them had to do with lower extremity muscle strength -- was not able to show any increase in dystrophin in those biopsies.

So I felt like the negative results or mostly unimpressive results weakened my perception of the trial results. And I would also make sure to echo what Dr. Nuckolls and Mr. Cassidy had to say about boys who are undergoing biopsies that either were not biopsying the correct muscle or in the correct way, or were then subsequently not handled in a way that they could be interpretable. And I think that that's something to take into account in future studies.

DR. ROMITTI: Paul Romitti, and I voted C, no effect. I did that mostly because I recognize it's complex to measure biomarkers in general; if you don't recognize the right compartment at the right time, you can obviously get erroneous results.

I think that the results to me are inconclusive enough, and I think there's enough missing data, as Dr. Nuckolls points out, that it's

concerning. So I don't think we have a good sample here to really base our results on. And I agree with Dr. Levine that even if we go ahead and use the data we have and what's available to us, maybe it really is telling us what study 3 is telling us, that there's no effect.

So if I had to go that way, it's not going to influence my interpretation of the clinical data. I just don't think the data are strong enough to make a strong interpretation.

DR. ALEXANDER: Thank you very much.

We'll move to the final question, which is question 9. In light of today's discussions, please discuss the overall strengths and weaknesses of the data supporting the efficacy of drisapersen and the acceptability of its safety profile for the treatment of Duchenne muscular dystrophy and amenable to exon 51 skipping.

So among other things, this is an opportunity to address a previous question that came from the committee regarding when we could talk about the totality of evidence.

Dr. Green?

DR. GREEN: An argument that's been thrown around is that it's used in a narrow group of people who are not under a rapid decline. And if so, we'd better define that group, like in Alzheimer's drugs, where it may be of value in a certain age group or disease progression, and we'd better know that.

DR. ALEXANDER: I'm sorry. Did you say who are under rapid decline or who are not?

DR. GREEN: Who are not.

DR. ALEXANDER: Who are not under rapid decline.

DR. GREEN: Right. So it may be a very narrow range window where it's effective.

DR. ALEXANDER: Dr. Onyike?

DR. ONYIKE: I'll start with the safety. I think the families and the people who suffer this illness have spoken eloquently about the safety issues and what they will accept. So I'm quite comfortable sitting with that.

Now, in terms of the data itself, one of the

concerns that still is at the back of my mind is what I think is probably some degree of oscillation or variability in the course over time, say from clinic visit to clinic visit.

Just to reference what I'm more familiar with, in dementia, for example, we know that there's variability in the mini-mental state exams scale, just to use that one particular, from visit to visit, might not necessarily represent progression in the neurodegeneration.

So I think that some clarity about this issue is pertinent to reconciling the data that we've been evaluating with the reports from the families. I don't know if there are methodological ways -- perhaps some reconsideration of the kinds of measures that are being used in the field.

But what we have in front of us, I think, is, as Dr. Zivin had so clearly expressed earlier, not yet ready. So that's my view.

DR. ALEXANDER: And just to be sure I'm clear, in highlighting the variability within an individual over time, are you trying to accentuate

or emphasize the measurement challenges that that represents, or the endpoints? Or how should the FDA and sponsor consider that going forward?

DR. ONYIKE: Well, there are a number of things. Firstly, what you've just spoken to the issue of endpoints, I think we can all relate to that very easily. Also, the issue of perceptions, so when people go to a visit, get randomized, go home, have an improvement, is this something that might have occurred anyway? So that needs to be understood, I think.

DR. ALEXANDER: Thank you.

Mr. Cassidy?

MR. CASSIDY: I have to say I still have some concerns about the safety profile for the sponsor, actually. And I don't mean to get too deep into specifics. But I'm still concerned about this patient that experienced cranial venous sinus thrombosis.

I'm a little bit puzzled about the explanation for this. On page 38 of BioMarin's briefing document, the core document, it suggests

it has to do with concomitant use of dipyrone, and was the patient on dipyrone prior to the seizures and CVST?

Because in the appendix, I see seizures on December 13th and then it's not mentioned until December 17th, when the CVST is identified, that he's being treated with dipyrone. So was he on dipyrone prior to the seizures and CVST and then more was added?

DR. ALEXANDER: Thank you for that comment, which we'll note on the record. I don't know if the sponsor wants to address that particular issue or not. The question was just whether the patient was on, I believe, study drug at the time that he or she -- he, excuse me -- experienced central venous sinus thrombosis.

Could you announce who are as well, please?

DR. NOONBERG: Sarah Noonberg, head of clinical development at BioMarin. The patient had received dipyrone intermittently. The patient was not on that medication at the time of the event.

DR. ALEXANDER: Thank you.

I'd like to ask about mortality. It's something that we haven't really discussed except for there was a brief comment in passing earlier about it. So my understanding from the sponsor was that there were no deaths during the clinical development program. But if I understood the FDA, there was a comment from Dr. Farkas mentioning something about mortality. So I would be interested to know that.

DR. FARKAS: Yes. I'd like to clarify. I agree there was no mortality during the study. I think that what Dr. Mentari was trying to get across is that but by a hair, I guess, there is the risk of mortality from these adverse events, and that -- this could be, again, a matter of discussion -- well, I guess the bottom line, I'll just say, is that if there were more patients who experienced these adverse events, some would have died.

DR. ALEXANDER: Dr. Mielke?

MR. CASSIDY: Chris Cassidy. One more question about the patient with the CVST. Another

possibility that BioMarin offers in its data on page 38 is that it might have something to do with the hypercoagulability of his blood, a common complication of DMD.

Admitted, I had never heard of this before. And I asked around the community, and I still hadn't heard a whole lot. I have read the Toshio Saito study cited -- well, he cited coagulation and fibrinolysis abnormalities in patients with muscular dystrophy.

But it doesn't seem terribly common. So I was just hoping to maybe hear a little bit more about that explanation.

DR. ALEXANDER: Does the sponsor want to briefly address that? I think the question is about hypercoagulability associated with the study drug.

DR. NOONBERG: Yes. This is a rare event. We do believe that muscular dystrophy is associated with a chronic inflammatory state, and in children, a venous sinus thrombosis, the biggest risk factor is connective tissue disorders and other chronic

inflammatory states. And the patient did have an elevated, high sensitivity CRP at the time of screening.

So again, we can't put all of the pieces together. We've also seen reports that hospitalized patients, approximately 20 percent of hospitalized patients, have a thrombotic event.

So we believe that Duchenne is associated with a chronic inflammatory state, and that muscle degeneration leads to activation of the coagulation cascade, again at a very low level and over a long period of time. But that's what we believe the risk factor is for that patient.

DR. ALEXANDER: Thank you.

We have just a few minutes remaining. So maybe if there's discussion, really, globally, this is an opportunity to discuss, in addition to specific safety concerns or questions about efficacy, more broadly how the overall strengths and weaknesses of the data supporting the efficacy of the product and the acceptability of its safety profile for the treatment of this disorder.

Dr. Mielke?

DR. MIELKE: I agree with Dr. Onyike about the safety. I think given the progressive fatalness of the disease, that it really goes to the individuals and the parents who try and understand what's best for them. I think the phase 3 results were disappointing in light of some of the promise of the initial studies.

However, I do think there are suggestions that it may be beneficial for some individuals, and that we need to try and understood -- and more work needs to be done to try and understand -- which individuals those are that will be helped the most.

There still hasn't really been as much of a discussion about trying to go earlier as well, and also looking at individuals or children less than the age of 5 and to see if they're helped more.

DR. ALEXANDER: Thank you.

Dr. Zivin?

DR. ZIVIN: I've just really said everything that I need to say.

DR. ALEXANDER: Thank you.

Dr. Romitti?

DR. ROMITTI: Yes. I just want to go back to looking at the totality of evidence since I brought that up. There seem to be differences and disagreements, perhaps, if that's not too strong a word, between post hoc analysis run by the sponsor and those run by the FDA. And unfortunately, we didn't get a chance to delve into those today.

So I'll leave this as a comment rather than a question. The comment I have is when I look at the sponsor's information, they seem to pool either all the studies or studies 1 and 2, which are phase 2. And I understand and I recognize the different designs and the different intents.

But I still go back to the loading dose issue, and I guess I don't know if the sponsor really pooled studies 2 and 3, which had the study design from the aspect of a loading dose, and what they found. Granted, study 2 is a small sample size compared to study 3. But it would have been interesting to look at that.

I would encourage that. And given my

experience in studying Duchenne muscular dystrophy, I would agree with the comments by Dr. Mielke. There probably are subgroups that can benefit from this.

What I would like to see, and I hope others, is that by changing some of these to science and looking at the loading dose, might we even improve the older patients, and we get to our general population sample, and we have a phase 3 trial like that. I just still wonder what difference that would have made.

DR. ALEXANDER: Dr. Nuckolls?

DR. NUCKOLLS: I think the positive experiences of Gavin and Jacob and Maxime and others makes me think, well, is it possible that there is a small subset of super-responders in this group, perhaps because of genetic modifiers or other factors?

It looks from the data that there may be some evidence of that in the phase 2 trials, but not so much in the phase 3 trial. But I think that's something that needs to be considered, given

the compelling cases that we've heard from the boys today.

DR. ALEXANDER: Dr. Kesselheim?

DR. KESSELHEIM: Yes. I just wanted to add just a little bit more to what I thought was an excellent summary by Dr. Mielke earlier about the benefits and the risks of this. Obviously, we're talking about a substantial unmet medical need here.

But if we're talking about a subgroup, if we're thinking that maybe the subgroup that will be most responsive to this drug here is the younger patients or patients with preserved function, then you don't need to think about the balance of how the risks might look in that patient population, where they're still highly functional, at a point in their lives at which they're still highly functional. And then taking on the risks of the medication may present a different balancing than what we're currently seeing in the phase 3 trial.

So I think that that sort of analysis remains to be done, and that balancing needs to be

done by the investigators and families. And I think the results of that remain to be seen.

DR. ALEXANDER: Thank you.

We'll just take two more, and then I'll try to summarize. Dr. Levine and Ms. Gunvalson.

DR. LEVINE: Very briefly, I agree with Dr. Onyike that the presentations by parents and patients make very clear that they can understand the safety issues. And as a pediatrician, I think that given the clear outcome of muscular dystrophy, that they should be allowed to make the safety decision if the drug is efficacious.

It seems to me, taking the totality of the information that we've had, the analysis by BioMarin and the FDA, efficacy has not been established.

DR. ALEXANDER: Thank you. And Ms. Gunvalson?

MS. GUNVALSON: I want to add a bit to what Dr. Nuckolls just said. Clearly, some of the boys are responding. And when you talk about the younger boys responding better, I think you need to

take into consideration that there are 20-year-olds who are in better shape than 12-year-olds with this disease.

There is variability. And so to just put an age on something, I think, is not fair. I know several boys who have died in their teens, and I know several that are doing real well in their 20s.

So just to take some thought in that. And for a 16-year-old, to stabilize would be huge. It's not always to get better, but even to stabilize at that age.

DR. ALEXANDER: Thank you very much. Thank you, everyone. I'll try to summarize question number 9 discussion for the record.

There was a comment that the product might be able to be used in a narrow group of people who are not under rapid decline, but that it was important to define who would comprise this group.

Patients and families have spoken eloquently about the safety issues and what they would accept.

There is variability in the condition visit to visit. It may not represent irreversible

decline. But this is important in understanding, as decisions are made regarding endpoints, but also perceptions of patient improvements as changes visit to visit occur.

There are concerns about the safety profile, the patient that experienced venous sinus thrombosis in particular. There was some puzzlement about the explanation for that and clarification as to whether or not the patient was on study drug at the time this occurred. A point was made that this disease is associated with a chronic inflammatory state, which is also a risk factor for venous sinus thrombosis.

There were no mortalities during the study, although some of the adverse events have a risk of mortality. And there was a suggestion that if there were more patients who had experienced certain adverse events, one or more may have died.

The progressive and serious and fatal nature of the disease, if untreated or with currently available treatments, was highlighted, and safety concerns were felt suitably left to patients and

their families.

The phase 3 study, the third study results, were disappointing. But there was some suggestion that the product may be beneficial for some individuals. There was also encouragement to look at children less than 5 years of age.

The sponsor, when aggregating data, appeared to aggregate, in some cases, all of the study results, and there was a question or encouragement to consider looking at just those which lacked a loading dose.

There was hope expressed that changing study designs and looking at a loading dose, one may be able to identify more uniform or robust improvements in the primary outcomes.

There was a possibility that a small set of individuals may be super responders, and that this needs to be considered, given the compelling cases we've heard from the public, a substantial unmet medical need.

A point that the risk/benefit balance, if we're talking about a subgroup that's younger or

those with preserved function, that the risks and risk thresholds or tolerance may be different also among them, and so this has to be balanced.

Presentations make clear that patients and families understand the safety, and there was a belief that they should be allowed to make the safety decisions if the drug is deemed efficacious, which someone felt had not been established.

Another point made that age thresholds along are insufficient for stratifying treatment because there's so much variability, even among patients of the same ages.

So I believe the FDA may wish to have a final comment. And as the chair, I would just like to thank the FDA and the sponsor, patient representatives, patients, members of the general public and other guests, for all of the incredible amount of work and thought that goes into all of the work that was discussed today and that goes into making an event like today possible.

So thank you very much, and I'll pass it to the FDA if there are any final comments.

DR. DUNN: Thank you, Dr. Alexander. Just very briefly, I echo your thanks to all those you cited as well as to the committee itself.

Perhaps before thanking the committee, I'd like to reiterate what I said this morning. I'd like to both personally and on behalf of the FDA offer our most sincere appreciation, in particular to the DMD patients that were here today.

The efforts and sincerity that you brought to your testimony today is very important, and we really do express our gratitude to you for that, as well as to the family members and caregivers of patients with DMD. Thank you very much for being here.

To the committee, thank you for your important work today. This has been very illuminating. It's been very helpful. As I said at the outset of this meeting, we come to you with a very open mind, notwithstanding the fact that a great deal of review work has already been done. And we listen carefully to your comments and will incorporate them into our continued decision-

making.

So with that, thank you very much. Dr. Alexander, thank you for chairing the meeting.

Adjournment

DR. ALEXANDER: Sure. Thank you.

We will now adjourn the meeting. Panel members, thank you again, and please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they may be recycled.

Thank you again. Have a good evening.

(Whereupon, at 5:31 p.m., the committee was adjourned.)