FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE (PCNS)

Monday, April 25, 2016
8:00 a.m. to 7:37 p.m.

College Park Marriott Hotel and Conference Center
Chesapeake Ballroom
3501 University Boulevard East
Hyattsville, Maryland
Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

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PROCEEDINGS

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning, and thank you for joining us today. I'd like to first remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Sandy Walsh.

Sandy, if you are present, can you please stand and identify yourself? Thank you.

My name is Dr. Caleb Alexander. I'm the chairperson of the Peripheral and Central Nervous System Drugs Advisory Committee meeting, and 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 with Dr. Gordon, please.

DR. GORDON: Good morning, everyone. My name is Mark Gordon. I am the industry representative, and I work for Boehringer Ingelheim
Pharmaceuticals.

DR. HOFFMAN: Richard Hoffman. I'm a pharmacist and medical writer, and I'm the consumer representative for this meeting.

DR. GREEN: Mark Green. I'm a professor of neurology, anesthesiology, and rehabilitation medicine at Mount Sinai School of Medicine.

MR. DUPREE: I'm Benjamin Dupree, a 23-year-old with Duchenne muscular dystrophy, here serving as a patient representative.

MS. GUNVALSON: I'm Cheri Gunvalson. I'm the mother of a 24-year-old son with Duchenne. I'm also a nurse and a clinical nursing professor at the University of North Dakota.

DR. KRYSCIO: Good morning, I'm Richard Kryscio. I'm from the University of Kentucky, and I'm a biostatistician.

DR. ROMITTI: Good morning. I am Paul Romitti, a professor of epidemiology and toxicology at the University of Iowa.

DR. NUCKOLLS: Good morning. I'm Glen Nuckolls. I'm program director for the muscular...
dystrophies at NIH at the Neurology Institute, and
I'm the designated federal official for the
Interagency Muscular Dystrophy Coordinating
Committee.

DR. FOLEY: Good morning. I'm Reghan Foley.
I'm a pediatric neuromuscular specialist. I work
at the Neuromuscular and Neurogenetic Disorders of
Childhood Section of the Neurogenetics Branch of
the NINDS at NIH.

DR. KESSELHEIM: Good morning. I'm Aaron
Kesselheim, an associate professor of medicine at
Brigham & Women's Hospital in the Division of
Pharmacoepidemiology and Pharmacoeconomics at
Harvard Medical School.

DR. ALEXANDER: And once again, I'm Caleb
Alexander. I'm an associate professor of
epidemiology and medicine at Johns Hopkins
Bloomberg School of Public Health.

DR. CHOI: Moon Hee Choi, designated federal
officer.

DR. ONYIKE: Chiadi Onyike, associate
professor of psychiatry at Johns Hopkins.
DR. GONZALES: Nicole Gonzales, associate professor of neurology at the McGovern Medical School at the University of Texas in Houston.

DR. OVBIAGELE: Bruce Ovbiagele, professor and chair of neurology at the Medical University of South Carolina.

DR. FARKAS: Ronald Farkas, clinical team leader at the Division of Neurology Products at FDA.

DR. DUNN: I'm Billy Dunn. I'm the director of the Division of Neurology Products at FDA.

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

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

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs in CDER at FDA.

DR. TEMPLE: Good morning. Bob Temple, deputy director of ODE-I.

DR. WOODCOCK: And I'm Janet Woodcock. I'm
head of the drug center 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 topic during breaks or lunch. Thank you.

Now I'll pass it to Moon Hee Choi, who will read the conflict of interest statement.

**Conflict of Interest Statement**

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting.
and to the public. FDA has determined that members
and temporary voting members of this committee are
in compliance with Federal Ethics and Conflict of
Interest laws.

Under 18 U.S.C. Section 208, Congress has
authorized FDA to grant waivers to special
government employees and regular federal employees
who have potential financial conflicts when it is
determined that the agency's need for a particular
individual's services outweighs his or her
potential financial conflict of interest.

Related to the discussions at today's
meetings, members and temporary voting members of
this committee have been screened for potential
financial conflicts of their own as well as those
imputed to them, including those of their spouses
or minor children, and for purposes of 18 U.S.C.
Section 208, their employers. These interests may
include investments, consulting, expert witness
testimony, contracts, grants, CRADAs, teaching,
speaking, writing, patents and royalties, and
primary employment.
Today's agenda involves new drug application 206488, eteplirsen injection for intravenous infusion sponsored by Sarepta Therapeutics for the treatment of Duchenne muscular dystrophy in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This is a particular matters meeting during which specific matters related to Sarepta Therapeutics NDA will be discussed.

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

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

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 participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ALEXANDER: Thank you very much. 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.

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

I'm in a somewhat unusual situation of delivering remarks that will, in part, be the same as or similar to remarks I made to this committee quite recently, when we gathered almost exactly five months ago, to discuss drisapersen for the treatment of Duchenne muscular dystrophy.

While perhaps familiar to some, I am certain that we have quite a few people joining us today who were not present in November of last year, and many of my comments bear repetition.

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 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. I am extraordinarily impressed with the turnout for this committee meeting as I look out over the audience today, and I was particularly impressed as I walked in through the public spaces of all the patients with DMD who are here. Thank you for being here. Your efforts to be here are invaluable and tremendously appreciated.

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, as many here know, from an advocacy group that was submitted to us for our consideration. I am happy to be able to
say that building on that effort, we published our
own draft guidance in June of last year for DMD, a
major accomplishment and I think a source of great
collaborative progress for the field.

We are here today, after a delay due to
severe weather in January that has tried the
patience of many, to discuss eteplirsen 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 disease. We are highly
sensitive to the urgency needed for the development
of an improved treatment for Duchenne. Before
briefly describing some of the issues we will ask
you to discuss today, I want to stress that we have
not made any final decisions on the approvability
of this application.

Many believe that we are here today to
render a final decision on approvability. We are
not. We are here to have a discussion and gain
input from you, the committee members.

The information in your background packages are preliminary reviews only that do not yet take into account today's proceedings. Though you may encounter preliminary conclusions and recommendations concerning approvability and, as you have seen in your background materials, they may often describe grave concerns about the data put forth in support of the ostensible effectiveness of eteplirsen.

Those conclusions and recommendations should be viewed as just that, preliminary. They should not be viewed as the opinion or conclusion of anyone other than the author of the individual review, and they should not be viewed as necessarily indicative of our final decision.

The reason we are here today is to gain your input into some of the 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, eteplirsen 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 eteplirsen is designed to produce could be helpful is an open question. The committee will recall its previous discussion in November during which the committee expressed concern about the plausibility of clinical benefit being derived from extremely small increases in dystrophin on the order of post-treatment absolute values of less than 1 percent of normal.

As you will hear today, we are again confronted with post-treatment absolute values in that range.

You will also hear of concerns concerning limitations on the interpretation of these post-
treatment absolute values. Of possible relevance to this question of how much dystrophin could convey clinically meaningful benefit is the fact that some patients with Duchenne have very small amounts of the naturally occurring truncated dystrophin that does not appear to be associated with an appreciable slowing of muscle degeneration.

Some patients with a related form of muscular dystrophy, Becker muscular dystrophy, naturally produce such a truncated dystrophin and have only mild disease. In these Becker patients, the truncated dystrophin is present at levels often 50 to 100 percent of what normal dystrophin would be.

The sponsor conducted three studies of eteplirsen, two small exploratory studies, which are referred to as study 28 and study 33, to assess the potential of eteplirsen to increase dystrophin expression, and a single small 12-patient clinical study, which is referred to as study 201/202 but is really a single study with two phases, to further assess the extent to which eteplirsen might
increase expression of dystrophin and to explore the potential clinical benefit.

As I said, though an initial phase of study 201/202, the 201 portion, was placebo-controlled, dividing the patients into 3 groups of 4 patients each, the second phase of the study was an open-label extension.

Despite strong encouragement from FDA to conduct an adequately powered, randomized, placebo-controlled trial or trials to assess the clinical effect of eteplirsen, the sponsor asserted that the conduct of such a trial would be prohibitively difficult.

Given the sponsor's assertions, FDA advised the sponsor on the issues involved in an attempt to compare the open-label extension data to data from a natural history cohort identified post hoc that might serve as an external control, emphasizing that interpretation of such a comparison could be difficult and that the acceptability of this approach would be a matter for NDA review.

The sponsor identified two DMD patient
registries, one in Italy and one in Belgium, as a source of external data, and conducted a post hoc comparison of the data from the open-label extension to data from these two registries.

The sponsor offers as primary support for approval a comparison of ambulatory ability based on 6-minute walk distance in these two groups. As is clear from the background documents provided to you, we have significant concerns about the validity of this comparison.

It is these two primary issues, one, the data concerning dystrophin, we will ask you to discuss and vote on whether there is substantial evidence from adequate and well-controlled studies as required under the Food, Drug, and Cosmetic Act that eteplirsen induces a production of dystrophin to a level that is reasonably likely to predict clinical benefit.

Two, the data concerning the historically controlled comparison of ambulatory ability, we'll ask you to discuss and vote on whether substantial evidence of effectiveness has been provided as
required under the Food, Drug, and Cosmetic Act by
the clinical results of a single historically
controlled efficacy study. It is these two issues
that we primarily bring to the committee for your
discussion.

Why do we focus on these two issues in this
manner? We must, as required by law, determine
whether there is substantial evidence of
effectiveness of eteplirsen in order to consider
approval. Both of these issues have the potential
to provide such evidence if the data are
interpretable.

Substantial evidence of effectiveness is a
crucial concept and one worth spending a few
moments discussing. Prior to 1962, evidence of
effectiveness was not even required for drug
approval, it was only necessary to demonstrate
safety.

The 1962 Kefauver-Harris amendments to the
Food, Drug, and Cosmetic Act included a provision
requiring manufacturers of drug products to
establish a drug's effectiveness by substantial
evidence, an important advance that signaled the beginning of the modern era of drug development and regulation.

Senator Kefauver considered these amendments requiring evidence of effectiveness his finest achievement in consumer protection, and their adoption laid the groundwork for FDA's development of an evidence-based model for drug evaluation decisions that stands as the global standard. Their importance is impossible to overstate.

"Substantial evidence of effectiveness," these words are not vague words to be defined according to whim or fashion. Substantial evidence was defined in Section 505(d) of the Act as, quote, "Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could be fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have
under the conditions of use prescribed,
recommended, or suggested in the labeling or
proposed labeling thereof." It's a mouthful, but
that's what it is.

Adequate and well-controlled investigations
are further defined in FDA regulations as having
various characteristics, one of which is the use of
a design that permits a valid comparison with a
control to provide a quantitative assessment of
drug effect. Of the generally recognized controls
that are recognized in regulations, all are
concurrent except for the last one known as
historical control.

The regulations note that, quote, "Because
historical control populations usually cannot be as
well assessed with respect to pertinent variables,
as can concurrent control populations, historical
control designs are usually reserved for special
circumstances.

"Examples include studies of diseases with
high and predictable mortality, for example certain
malignancies, and studies in which the effect of
the drug is self-evident, for instance general anesthetics or drug metabolism."

You will note that investigations are referred to in the law, investigations being plural. It has long been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.

The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

Any clinical trial may be subject to unanticipated, undetected systemic biases. These biases may operate despite the best intentions of sponsors and investigators and may lead to flawed conclusions.

There are circumstances in which FDA may
rely on something less than at least two adequate and well-controlled studies. In 1997, the FDA Modernization Act, which we refer to as FDAMA, amended Section 505(d) of the Act to make it clear that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.

Reliance on only a single adequate and well-controlled efficacy study to establish substantial evidence of effectiveness is also a possibility. Because reliance on two adequate and well-controlled studies is generally more secure than reliance on one similarly persuasive study, FDA has generally relied on only a single adequate and well-controlled efficacy study to support approval only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have
been difficult to conduct on ethical grounds.

Examples of typical characteristics of a single adequate and well-controlled study that could make the study adequate to support an effectiveness claim include those that you see here. These are examples, they are not requirements, but they have a common theme in that such characteristics serve to increase the reliability of the reported findings and might allow the results of a single study to effectively provide a similarly persuasive amount of information as two independent adequate and well-controlled studies.

Because of the inherent vulnerabilities involved in reliance on a single study, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single trial.

Generally, when discussing substantial evidence of effectiveness, we are discussing evidence based on primary assessment of clinically
meaningful effects, and such substantial evidence may result in a conventional approval.

Accelerated approval is a particular type of approval that FDA may grant to a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and is reasonably likely to predict an effect on such; or some other clinical benefit taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

FDA has discussed accelerated approval in the context of DMD specifically in our DMD guidance that I mentioned earlier. We have indicated that biomarkers that reliably reflect the health and amount of skeletal muscle may, if supported by sufficient scientific evidence and acceptable analytical methods, be used as endpoints to support
accelerated approval of a new DMD drug. Such a biomarker would have to be reasonably likely to predict clinical benefit in order to be acceptable as a basis for accelerated approval.

Concerning accelerated approval, it is crucial to recognize that the evidentiary standards for effectiveness are not lower for biomarker or intermediate clinical endpoints used to support accelerated approval. Substantial evidence of an effect on those biomarker or intermediate clinical endpoints must be demonstrated.

As we discussed, substantial evidence comes from adequate and well-controlled investigations and is evidence that the drug will have the effect it purports or is represented to have. Accelerated approval concerns the character of the endpoints, not the strength of the results on those endpoints.

An effect on an endpoint supporting accelerated approval must be an effect on an endpoint that in its character is reasonably likely to predict clinical benefit, and in its persuasiveness provide substantial evidence of
effectiveness from adequate and well-controlled trials just as substantial evidence of effectiveness on a clinically meaningful endpoint from adequate and well-controlled trials supports conventional approval.

It is a common misconception that data not sufficiently persuasive for conventional approval can be shifted over to consideration for accelerated approval. Accelerated approval is not a rescue strategy for suggestive data that are insufficient for conventional approval.

Although it is possible to consider suggestive data, insufficient on their own for conventional approval, in a supportive role to complement substantial evidence of effectiveness that has been provided for a biomarker, accelerated approval cannot be used to compensate for weak or inconsistent clinical findings.

It is more common to consider accelerated approval when data on the biomarker are available in advance of clinical results. If unconvincing clinical results are reported in the face of what
are thought to be promising biomarker results, this would tend to weaken confidence that the biomarker results are reasonably likely to predict benefit.

As I mentioned previously, under the proper circumstances, FDA regulations recognize that historical control studies can be considered adequate and well-controlled studies and used to support approval. There are many issues to consider with the interpretability of such studies as discussed in an international guideline concerning choice of control group in clinical trials.

These issues are of critical importance when considering any historical control trial, and so Dr. Bob Temple will present a separate discussion of this important topic that will help inform issues specific to the eteplirsen application that will be subsequently discussed by the review team.

Following my remarks, the applicant, including consultants from the academic and advocacy arenas, will make a series of presentations supportive of eteplirsen's benefit,
and you will have a chance to ask clarifying questions.

After a short break, we will reconvene for a series of presentations from the FDA, beginning with comments from Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research.

Next, as I noted, Dr. Temple, the center's deputy director for clinical science and the acting deputy director of the Office of Drug Evaluation I, will discuss issues to consider with external control studies.

Following that, Dr. Ron Farkas, a team leader in the neurology division, and Dr. Ash Rao, the acting chief of the Laboratory of Applied Biochemistry, will present a detailed discussion of the multi-disciplinary team's concerns and findings regarding the eteplirsen application.

Dr. Eric Bastings, the neurology division's deputy director, will provide concluding remarks. You will again have a chance to ask clarifying questions.

After a break for lunch, we will have the
open public hearing followed by discussion and questions to the committee. The FDA presentations will highlight a number of issues that we'll ask you to discuss and respond to, including the strengths and weaknesses of findings regarding dystrophin, the strength and weaknesses of the clinical findings, the relative impacts of various clinical outcome measures that were assessed, and of fundamental importance, the comparability of the eteplirsen and control groups. We have provided discussion topics and questions to help frame your discussion following the presentations.

As you consider the background materials, I remind you that we have been made aware that some of you have been approached by outside organizations; some of you on the committee have received materials that were ostensibly germane to these proceedings.

I think you've been informed by the advisory committee staff, and I've been asked to remind you, that you are to consider only the background documents that were provided to you by the
applicant and by the agency, not any other materials that were provided to you by outside agencies.

I urge the committee to keep several things in mind as the remainder of the meeting gets underway. It might fairly be asked, although you say no final decision on approvability has been made, isn't that disingenuous. Your background materials are highly critical and you describe fundamental concerns about the application. Why was this even accepted for review?

It is important to note that when we were involved in discussions with Sarepta about application submission, it was our understanding that dramatic increases of dystrophin were being observed, as much as 50 percent of normal values, and that this was accompanied by dramatic and unprecedented clinical stabilization of patients. Such reports, unless obviously dismissible on face, clearly would warrant careful review.

An important, perhaps the important, issue we bring to you for discussion, is comparability.
You will hear both scientific and emotional commentary and testimony about how eteplirsen treated patients are doing. We do not challenge that. The concerns we raise about the application are not trying to suggest that what these patients are reporting, completing, achieving, living is not real. It clearly is.

What we are concerned about is the accuracy and acceptability of the comparison being made to a group that could differ in important ways, both known and unknown, from the eteplirsen treated patients.

Please, as what will surely be an emotional discussion might tend towards a suggestion that we, the FDA, do not accept these reported improvements as important, know that if these results were from a well-designed, interpretable trial, there likely wouldn't be much to talk about. We likely wouldn't even be here.

We come to you with sincere concerns not because we take some perverse delight in keeping new medicines from those who urgently need them, as
has been somewhat bizarrelly suggested by some, but because it is our, we the FDA, and you our advisory committee, collectively, it is our fundamental responsibility to ensure, as required by law, that the treatments we approve are effective.

Keep your focus on the comparability of these groups and whether we can truly conclude that what these few eteplirsen treatment patients are experiencing is clearly outside the natural variability of the disease.

There are many people here. It's extraordinarily important that everybody that has come is here, and it's extraordinarily important that those who are watching from afar are doing so. As Dr. Alexander noted, it's entirely possible that emotions will run high. People are passionate and invested, and we understand that.

Investment can influence perception. I have no doubt that if I had DMD and I was receiving eteplirsen, that I would attribute all of the success of my activities to eteplirsen. I may be right about that. The issue is whether or not we
have a group to which we can compare reliably.

   I am truly glad everyone is here. The
outpouring of support for those with this disease
is nothing short of spectacular. It provides
needed context and awareness, but anecdote and
emotion do not change the data with which we are
confronted, no matter the attendance.

   Whether we have 1,000 here or only 1, the
same data will be there to consider. And I know
that each of you will render the same
scientifically sound opinions and judgments to a
full room that you would to an empty one.

   Speaking of a full room, even as I am deeply
moved by those here in attendance, it makes me
realize that I have a message for those, many who
are watching these proceedings, both with Duchenne
and even for illnesses other than Duchenne,
especially diseases that occur only in small
numbers, and those folks who have diseases that do
not have highly organized support systems and
advocacy machines capable of assembling such a
massive effort as that which we see today.
It must be frightening to think that there is no way that you can be heard. I want to reassure you, it is not the volume of the message, but the content. We listen, and we listen closely. To all those out there watching, your voice is heard.

We have brought to you important issues for which we seek your advice. These are complicated issues, and we will be asking you to vote on several questions, and we'll be listening very carefully to your discussion of all these topics. The content of your discussion and explanation of your reasoning is of great importance to us.

Again, 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. It is vital.
Dr. Alexander, thank you for the time to offer my comments, and I return the proceedings to you.

DR. ALEXANDER: Thank you, Dr. Dunn.

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 interest 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 Sarepta Therapeutics presentations.

**Applicant Presentation - Shamim Ruff**

MS. RUFF: Dr. Alexander, members of the advisory committee, and FDA, good morning. My name is Shamim Ruff. I'm the head of regulatory affairs and quality at Sarepta. I am honored today to begin our formal presentation on eteplirsen for the treatment of Duchenne muscular dystrophy, or DMD.

Before we begin, however, permit me two brief but important acknowledgements. First, those who suffer from DMD, many of them here today, and in particular the 12 boys who allowed us to follow them for 4 years in our trials, this important dialogue today is for you.

Second, to those so deeply committed to combating this crippling disease, including caregivers and investigators, we thank you for your continued commitment.
We at Sarepta fully recognize that what we are about to present to you is not a traditional data set. It must be understood that DMD is an enormously challenging disorder to study due to its rarity, heterogeneity, and rapid progression. Nevertheless, in that context, we believe we have done both important and groundbreaking work.

Our colleagues at the FDA have understandably challenged us on several fronts. We both appreciate and welcome that challenge as it has caused us to think more deeply about DMD and we believe raises important questions for future research.

Today, we will address the key issues head on and offer you data that demonstrate three important findings.

First, eteplirsen unequivocally produces de novo dystrophin protein. Second, the external control is valid, reliable, and reflective of the natural history of DMD. And third, eteplirsen treated boys behave differently to DMD natural history with a large magnitude of benefit on the
6-minute walk test as well as loss in ambulation.

We look forward to a robust, scientific, and candid discussion and thank the panel for your participation in helping us advance the understanding of this disease.

DMD is a pediatric X-linked recessive neuromuscular disease caused by mutations in the DMD gene that prevent the production of functional dystrophin protein. Dystrophin plays a vital role in the structure, function, and preservation of muscle cells, and in its absence, patients follow a predictable disease course.

Boys develop muscle weakness in their first few years of life, then in early adolescence lose the ability to walk. Complications from this loss of ambulation have a major cascading effect, including scoliosis, compromised respiratory function, and premature death, usually in the mid-to late-20s.

As you will hear in a moment from Dr. Mercuri, despite welcome improvements in the standard of care, including steroids and other
supportive measures, there is a profound unmet medical need for DMD patients with no approved therapies in the United States.

The proposed indication for eteplirsen is for the treatment of DMD patients with mutations in the dystrophin gene amenable to exon 51 skipping. The proposed dose is 30 milligrams per kilogram, administered as weekly IV infusions.

Here's a breakdown of the genetic mutations for the 9 to 12,000 boys who suffer from DMD in the United States. The dark blue section indicates a subset of DMD boys who are amenable to skipping exon 51 and can be treated with eteplirsen. This represents 13 percent of the total DMD population and shows how eteplirsen is one of the first examples of precision genetic medicine.

In order to understand how eteplirsen works, let's look at the underlying disease process and how the drug addresses it. Here's a small section of the dystrophin gene where we see a normal reading of the mRNA by the ribosome, which in turn produces a dystrophin protein of normal length.
But here's what happens in a DMD patient, deletion mutations in the dystrophin gene disrupt the reading frame; thus, the ribosome can't correctly read the message after the deletion, which results in little to no dystrophin, the hallmark of the severe DMD phenotype.

Eteplirsen induces a skipping of exon 51, restoring the reading frame and allowing the production of a shorter, internally deleted, functional dystrophin protein.

As I previously mentioned, Sarepta comes to you today with a non-traditional data set, a small study with a natural history comparator. Yet, while the package may be unusual, it is not unprecedented in the rare disease arena. Of note, although the study size is not extensive, it is a 4-year clinical follow-up period that gives us both robust insight into the benefit of eteplirsen.

So how did we arrive at this point? Over the past couple of years, we've participated in more than a dozen meetings with the FDA to agree on an appropriate data package for an NDA submission.
Let me highlight a significant series of events that transpired during that time.

First, due to the initial encouraging results of our phase 2 study, the DMD community expressed an unwillingness to participate in a placebo-controlled study. This led FDA, in April of 2014, to ask us to obtain natural history or external control data for comparison. We did so, and comparison to that untreated external group now serves as the primary basis for establishing clinical efficacy.

In December 2015, the agency made a request for an additional 4-year data. The results were striking with a 162-meter benefit in the 6-minute walk test. In addition, Kaplan-Meier estimates showed a 17 percent loss of ambulation for eteplirsen compared to 85 percent for the untreated external control.

Because of this new and important data, FDA in February of 2016 extended the PDUFA date by 3 months. In recognition of this unique set of circumstances, Sarepta is seeking accelerated
rather than full approval.

FDASIA, the Food and Drug Administration Safety and Innovation Act, was signed into law in July of 2012. It expands and encourages the broader use of accelerated approvals beyond HIV and oncology to rare diseases such as DMD.

Importantly, FDASIA also requires FDA to seek patient input during drug development as well as during the review of the application. Of note, accelerated approval allows for an acceptable degree of uncertainty regarding the anticipated benefit.

Essentially, there are three specific requirements of accelerated approval, and eteplirsen meets them all. First, the disease has to be serious and life-threatening and the drug has to provide benefit over existing therapies. We clearly meet this.

Second, approval must be based on either a surrogate endpoint or an intermediate endpoint that are reasonably likely to predict benefit. For eteplirsen the FDA provided us two pathways, either
dystrophin as a surrogate endpoint or the 6-minute walk test as an intermediate endpoint.

Lastly, post-marketing confirmatory studies are required to verify the anticipated effect. Sarepta in consultation with the FDA agreed to conduct two post-marketing confirmatory studies.

We recognize that accelerated approval does not change the statutory requirements, and today we will demonstrate to you that the endpoints selected are appropriate and we have established substantial evidence of effectiveness.

So what constitutes substantial evidence of effectiveness? It's important to note that the intent of the statute was to reduce the chance of an incorrect conclusion. Ideally, a randomized placebo-controlled study would be used, but this is not essential.

Historical controls can be considered adequate and well controlled, particularly in the rare disease arena, and there are multiple examples of FDA approvals based on small studies and historical controls.
Before we go through the rest of the presentation, I'd like to address a few of the concerns FDA raised and offer our position beginning with dystrophin. First of all, in the week 180 analyses, FDA only focused on the Western blot results and discounted the immunohistochemical results.

Experts suggest there is no single definitive method for dystrophin quantification. Multiple complementary methods are required to get the full picture. Dr. Kaye will describe how eteplirsen showed significant dystrophin production using three distinct methods.

Second, eteplirsen Western blot results were compared to published references going back to 1989 that were semi-quantitative at best. The more appropriate comparison is to look at fold increases over baseline within the same assay.

Finally, they concluded that the quantity of dystrophin produced was not clinically relevant. However, research in the field suggests that even small amounts of dystrophin can have a clinical
effect. Of note, this is the first time that a therapeutic has demonstrated an unequivocal increase in dystrophin expression.

FDA also identified three main concerns with our 6-minute walk test results. First, they highlighted that study 201 failed to show an advantage over eteplirsen versus placebo for the 6-minute walk test at week 24. I'd like to clarify that percent dystrophin fibers was the primary endpoint for that study, not the 6-minute walk test.

They also outlined a concern about the use of external control to determine efficacy. The key issue here is the potential for bias due to differences in the two patient populations. To be clear, there were predefined selection criteria for the external control, which were based on the inclusion criteria for the eteplirsen 201 study.

Also, the key baseline characteristics were highly comparable, as were the standards of supportive care. They both had up to 4 years of longitudinal data, and 6-minute walk test
measurement was according to the same standardized protocol. The FDA guidelines also state that for an external control comparison to be interpretable, the effect size has to be large. We certainly saw a compelling effect size.

Finally, we will provide longitudinal comparisons to multiple databases that clearly show eteplirsen-treated boys behaved differently from natural history.

As you review the data we will present today, we ask that you keep an open mind and critically evaluate eteplirsen in context of accelerated approval, the rarity of the disease, and the profound unmet need. We know for certain that DMD boys, if left untreated, will progress in their disease with a known risk of serious and fatal consequences.

Given this, along with the production of de novo dystrophin protein and the benefits seen on the 6-minute walk test and loss in ambulation is the degree of uncertainty about whether the therapy will result in the anticipated clinical benefit
acceptable for accelerated approval.

Turning now to the rest of the agenda, we are extremely fortunate to have some of the world's eminent experts in DMD available today. In a few moments Dr. Mercuri, who provided much of the data for the external control, will provide an overview of the disease background and natural history.

Dr. Kaye, a pediatric neurologist and interim CEO at Sarepta, will present the efficacy data, followed by Dr. Eliopoulos, senior medical director, who will review the safety data. Dr. Mendell, the principal investigator for the pivotal eteplirsen studies, will provide a clinical perspective on the benefit-risk of eteplirsen. And finally, Dr. Kaye will return to provide concluding remarks.

In addition to answer questions, we also have available Dr. Muntoni and Dr. Wilton, who are two of the world's leading experts on dystrophin methodologies; Dr. Muntoni was also the PI for our phase 1 studies; Dr. Kinane, who is a pediatric DMD pulmonary expert; Dr. McDonald, who is a leading
DMD natural history expert in the U.S. and study
chair of the Synergy Duchenne Natural History
study; and last but not least, Dr. Lu, who is our
consultant statistician.

Please note that after the concluding
remarks by Dr. Kaye, there will be a presentation
by the Jett Foundation, who requested that we
donate a portion of our allotted time for a
separate and independent presentation. We are
happy to do so.

Christine McSherry, executive director of
the Jett Foundation and the mother of a boy with
DMD, will provide a review of the patient and
caregiver reported outcomes collected from
eteplirsen trials. And with that, I'm happy to
invite Dr. Mercuri to come to the podium and
describe the natural history of DMD.

Applicant Presentation – Eugenio Mercuri

DR. MERCURI: Thank you.

Good morning. My name is Eugenio Mercuri.
I'm a pediatric neurologist working in Rome and
coordinator of the Italian Duchenne network. I'm a
A Matter of Record
(301) 890-4188

paid consultant to Sarepta in preparation for this meeting, and I have no direct financial interest in the outcome of the meeting today.

As Ms. Ruff explained, Duchenne muscular dystrophy is caused by mutation to the dystrophin gene. In healthy boys, dystrophin is normally expressed and contributes to the protection of muscle fibers during contraction, acting as a molecular shock absorber. In DMD, the absence of dystrophin leads to progressive muscle degeneration with progressive loss of muscle function.

Here we see a series of muscle biopsies performed at different ages. The first picture on the left shows a biopsy performed at birth. Even though we know that dystrophin is already absent, the muscle tissue appears normal.

As shown in the second picture, already in the first years, there are aspects of inflammation and necrosis with loss of functional muscle tissue that increases over the years, and the major tipping point in the disease progression occurs around the age of 7.
At this age, you can see that muscle cells are increasingly replaced by fibrotic tissue and fat. Finally, in the fourth picture of a biopsy performed in an older boy, we see a complete loss of the normal muscle architecture.

Clinically, in the first month, there are no obvious clinical signs, but a blood test will reveal elevated CK levels, which is indicative of muscle damage. DMD boys often show some delayed milestones, but the diagnosis is on average after the age of 3 years. At a time when they are supposed to learn to hop, jump, and run, DMD boys have difficulty running and hopping, standing from supine, and in climbing stairs. After the age of 7, there is a more rapid decline leading to loss of ambulation in early adolescence.

Historically, before the era of steroids, DMD boys did not walk beyond the age of 12, with a median age at loss of ambulation of 9.5 years. Contemporary studies, however, have shown that the median age with current standards of care is between 11 and 13 years, and this is consistent
across countries.

Similar results were found in several U.S. and EU countries as well as in Japan. Recently, a new global data set from CINRG shows that the median age for loss of ambulation for boys amenable for skipping exon 51 is 12 years.

Loss of ambulation is an important endpoint, but we hear from Duchenne boys and their families that even after that, many other important physical functions are progressively affected. At loss of ambulation, boys are generally still able to perform shoulder movements, but later there is a progressive loss of upper limb function. And after the age of 20, arm movements are generally limited to distal movements of the fingers.

Respiratory impairment, which declines steadily throughout the patient's life, usually becomes significant enough to require nocturnal ventilation in the patient's 20s, followed by full-time ventilation. Heart muscle is also affected, and despite advances in care, most patients will die from cardiac disease in their
mid-20s. The mean survival is approximately 27 years.

Next, I'll talk about how disease progression is most commonly measured in clinical and research settings. The 6-minute walk test is the most widely used measure in Duchenne intervention or in natural history status. It's an integrated global measure that is affected by strength, endurance, and cardiorespiratory status. As you can see in the video, the test is performed by asking the patients to walk as fast as possible for 6 minutes around a 25-meter course, measuring the distance covered in 6 minutes.

The test has been slightly modified for children with Duchenne from the original American Thoracic Society version with introduction of a second examiner that stays close to the patient for safety reasons, as you can see on the video.

Another important modification is the use of standardized encouragement to maintain the child's attention and to limit bias. The examiner -- this is very important. The examiner must follow very
strict instructions providing the wording and the
timing of when the encouragement should be given.

In clinical trials and in natural history
status, experienced and trained physiotherapists
follow very strictly these procedures. As a
result, the 6-minute walk test has been found to be
a sensitive, reliable, and reproducible outcome
measures in a multicenter setting.

It also has the highest test/retest
reliability of the commonly used measure for
Duchenne. And another advantage of the 6-minute
walk test is its high correlation with other
functional measures.

In particular, it shows a correlation with
the North Star Ambulatory Assessment. The scale
was originally developed as a clinical tool for
ambulant Duchenne and has only recently been
validated as an outcome measure. Although it's
less statistically robust than the 6-minute walk
test, it provides important additional clinical
information.

The scale includes 17 items. Each item is
scored from zero, if the boy is unable to perform the task independently, to 2 if he's able to complete the task. The order of the items follows the progression of the disorder. Younger boys on steroids are generally able to complete most activities, but with increasing age, especially after the age of 7, they gradually lose abilities with the predictable disease course from bottom to top.

Focus groups with families made a strong point that each of the 17 activities are related to important activities of daily living and losing even one of them represents an irreversible loss that is important and meaningful for their quality of life.

Using these tools, we can measure sequential loss of function in Duchenne. For example, rise time is lost at early stage. It's actually the first activity that is lost when boys are still able to walk independently and perform the 6-minute walk test.

The 6-minute walk test provides a major
functional ambulation, and once boys are unable to complete the test, they are generally not able to walk outdoors or at school anymore. In some cases, the 10-meter test can be measured in these last stages of ambulation and can have a positive value at the time when they score zero on the 6-minute walk test. When happening however, this usually lasts only a few months. At this stage, they are usually only able to perform minimal functional walking at home, often holding on to furniture and walls for safety as the risk of falls and bone fracture is very high.

This has caused some confusion in the definition of loss ambulation with different definition in the literature. Moreover, this definition is more challenging in retrospective studies. For example, in the CINRG studies, which allowed for retrospective outcomes, loss of ambulation is defined as patient reported full-time wheelchair use confirmed by the 10-meter test when possible. In contrast, in many prospective studies, including the Italian Telethon and Leuven
studies, the loss of ambulation is defined as zero meters on the 6-minute walk test.

I will now review what we have learned from recent natural history data. Using the 6-minute walk test, we have been able to identify a number of prognostic factors affecting disease progression. The role of steroids is well-known, but recently, we have been able to identify other factors that affect the rate of decline, such as age, type of mutations, or the values of the 6-minute walk test.

As I mentioned earlier, boys with Duchenne initially gain in functional activity before experiencing a progressive and irreversible decline. In this study, 191 Duchenne patients were assessed at different ages and followed for 1 year. Patients who were younger than 7 when first assessed improved their 6-minute walk performance after 1 year by nearly 30 meters. In contrast, those who were older than 7 had already started declining by nearly 40 meters after 1 year.

This information has been extremely helpful
in identifying a more homogeneous declining patient population in more recent studies.

Let's focus on the group of 68 patients who were above the age of 7 when they were first assessed. In a follow-on study assessing 6 minute changes over 3 years, we not only confirmed that on average there is a decline in the first year, but also that there was progressive deterioration that became more marked with each increasing year.

In addition to age, genetic mutation has also been shown to impact performance on the 6-minute walk test. In this study of 191 patients with Duchenne, some differences in baseline 6-minute walk test were observed for different mutation types. The vertical line in the middle of the graph represents the mean values for the whole cohort. When we subdivide the cohort according to the type of mutation, all the different sub-groups were relatively close to the mean, but some differences could be observed. Patients with duplications or point mutations had better performance and on average walked more meters than
patients with deletions.

Some variations were also observed within the boys with deletions depending on which exons were deleted. Patients with exon deletions amenable to skipping exons 45, 51, or 53 all walked less far, indicating a more severe phenotype. In contrast, patients with deletions amenable to skipping exon 44 walked further at baseline.

This is consistent with other reports indicating a milder phenotype for this patient group, and it's probably related to the fact that these patients, unlike other groups with deletions, have low levels of naturally occurring dystrophin. This is also corroborated by a recent CINRG study, which reports that Duchenne patients with deletions amenable to exon 44 have a delay in loss of ambulation of up to 2 years.

As clinicians, we are often asked the question, why is it important to maintain 6-minute walk distance. And we have learned that maintaining 6-minute walk test is important because its distance can predict loss of ambulation.
This graph shows the results of a study performed on 131 boys with Duchenne followed for over 2 years. The study evaluated the risk of losing ambulation in different sub-groups subdivided according to the 6-minute walk test.

Looking from left to right, it's obvious that the risk of losing ambulation increases as the 6-walk distance decreases. These results suggested if we are able to maintain or even to slow down the degradation of the 6-minute walk distance, we therefore also decrease the risk of losing ambulation.

Maintaining ambulation is of course important per se, but it's also important as loss of ambulation is related to the onset of further progression of other aspects of disability. In a recent French study, a cohort of boys with Duchenne followed for over 20 years was subdivided into 3 groups based on age of loss of ambulation.

The study showed that boys who lost ambulation at the later stage, after the age of 11, also had a significant delay in the need for
ventilation and in the time when they lost the
ability to self-feed.

I would like to stress how important this
chain of events is. If we delay progression in the
6-minute walk test, we delay not only loss of
ambulation, but also the subsequent events of
disease progression, such as loss of self-feeding
or need for ventilation.

The natural history data I just showed are
the results of international efforts to harmonize
standards of care between U.S. and Europe that were
formally published in 2009. These include the use
of steroids, but also provides specific indication
on physical therapy and on the management of
orthopedic, respiratory, and cardiac risk.

In summary, the improvement in standard of
care has produced a clear shift in natural history,
delaying loss of ambulation and subsequent
functional decline, such as respiratory failure,
cardiac impairment, and ultimately death.

But this is not enough. Despite these
improvements, Duchenne is still a rapidly
progressive and ultimately fatal disorder. And as a clinician, as part of the Duchenne community, we strongly feel there is therefore an urgent unmet need to find treatments that may further slow down disease progression.

Now, I would like to turn the podium over to Dr. Kaye to discuss efficacy of eteplirsen.

**Applicant Presentation – Edward Kaye**

DR. KAYE: Building on the scientific foundation that Dr. Mercuri just presented, I would like to describe the findings that confirm eteplirsen benefit. We will look at the rationale for development of eteplirsen, an overview of Sarepta's clinical development program, a description of the pharmacodynamic data, the process for choosing the external control, the clinical results, and finally an overview of our confirmatory studies.

Let's begin by looking at the rationale for why exon skipping could work in Duchenne muscular dystrophy. As the previous speakers explained, mutations that disrupt the RNA reading frame lead
to the production of little to no functional
dystrophin and result in the severe DMD phenotype.

The concept of exon skipping as a
therapeutic strategy is demonstrated through an
experiment in nature. In Becker muscular
dystrophy, deletion mutations, which maintain the
RNA reading frame, enable the production of an
internally deleted dystrophin. These in-frame
mutations result in a shortened dystrophin protein
generally associated with a milder phenotype. Exon
skipping aims to produce a protein similar to
Becker.

FDA has stated in their briefing document
that Becker muscular dystrophy patients have high
levels of dystrophin, however, after looking at the
literature we note a wide range of dystrophin
levels, ranging from 2 to 100 percent.

Given this wide range of dystrophin
expression, researchers over the past 25 years have
tried but failed to establish a definitive
dystrophin threshold that results in a clinical
benefit. What has been established is that the
presence of even small amounts of dystrophin may have a clinical impact.

For example, Duchenne muscular dystrophy patients amenable to exon 44 skipping express slightly higher levels of dystrophin than the general DMD population and experience a milder phenotype. Ultimately, the most meaningful assessment of dystrophin in a clinical trial is not based on literature values but on increase from baseline. The conclusion was emphasized at a March 2015 FDA NIH workshop on dystrophin quantification, as well as in the FDA briefing guidance.

We are fortunate to have two academic experts with us today, Dr. Francesco Muntoni and Dr. Steve Wilton, who can answer questions and provide insight on dystrophin quantification.

I would now like to take a moment to review our complete DMD clinical program. Eteplirsen was initially evaluated in two phase 1 studies. The first established proof of concept through single intramuscular injection, and the second study tested weekly systemic IV administration at various
Having observed increased dystrophin in both phase 1 studies, Sarepta initiated study 201/202. This is the pivotal study, which will be the focus of my presentation today. Enrollment included an ambulatory population between the ages of 7 to 13 years.

To evaluate eteplirsen in a broader population, Sarepta is completing two additional phase 2 studies in both younger as well as more advanced patients. To support accelerated approval, the PROMOVI phase 3 confirmatory study is already underway.

In addition to eteplirsen, Sarepta has initiated two phase 1 studies with compounds that use the same chemical backbone but are designed to skip exons 45 and 53, respectively. The second confirmatory study is ESSENCE, which tests these follow-on compounds. I will further discuss these confirmatory studies at the end of my presentation.

Study 201 was a 24-week study to evaluate dystrophin expression as a pharmacodynamic
endpoint. The study tested eteplirsen at 2 systemic weekly IV doses, 30 milligrams per kilogram shown in purple, and 50 milligrams per kilogram shown in green, compared to placebo shown in gray. Dosing was limited to 8 patients at study initiation due to limited drug supply.

After week 24, the placebo group was rolled over on to either 30 or 50 milligrams of eteplirsen. Study 202 extended the trial to further evaluate both continuing pharmacodynamic and efficacy endpoints and is ongoing to date. Data from all 12 of these patients were pooled to enable comparison to an external control over 4 years.

In order to best observe a treatment effect, the 201/202 enrollment criteria were chosen to obtain a homogeneous group of patients that would be predicted to decline. As Dr. Mercuri detailed in his presentation, a number of prognostic factors predict decline in DMD, including a mutation amenable to exon 51 skipping, an age range of 7 to 13 years, a stable steroid regimen for at least
24 weeks prior to enrollment, and finally a 6-minute walk test distance between 180 and 440 meters. These same factors drove our enrollment criteria.

The pivotal 201/202 studies included several key endpoints. The primary endpoint for study 201 was increase in dystrophin protein expression. The primary clinical endpoint for study 202 is the 6-minute walk test.

Supportive endpoints included mechanism of action by RT-PCR, dystrophin protein production, the NSAA, and the ability to rise from supine. Importantly, we are here today to seek approval based on clinical differences in walking ability in addition to dystrophin production.

As I will now show, eteplirsen has a precise mechanism of action as demonstrated by dystrophin production. The most direct measure of eteplirsen's mechanism of action is exon skipping, which was evaluated by RT-PCR and sequencing. The shortened PCR product was identified and sequenced to confirm that the correct newly formed exon
junction was present. All biopsied eteplirsen patients produced the expected product, demonstrating that the drug is working as intended.

The March 2015 FDA NIH workshop on dystrophin measurement concluded that complementary methods are necessary to provide a complete protein assessment. Western blot was used to quantify dystrophin following extraction of protein from muscle tissue. However, for dystrophin to be functional, it must be localized to the sarcolemmal membrane and only immunohistochemistry can provide this information.

Immunohistochemical images were used to assess the percent dystrophin positive fibers providing information on sarcolemmal localization and distribution of dystrophin in muscle tissue. Finally, the immunohistochemical images were assessed by a computer algorithm to measure fluorescence intensity to quantify dystrophin at the membrane. Taken together, these assays provide a comprehensive view of dystrophin expression.

Study 201 was designed to test whether dose
or duration was most important in the production of
dystrophin positive fibers. No significant
increase was observed at 12 weeks for the
50 milligrams per kilogram cohort, but the endpoint
was met at 24 weeks for the 30 milligram per
kilogram cohort with an absolute change from
baseline and present dystrophin positive fibers of
13.7 percent with no increase seen in the placebo
group at week 24.

The FDA suggested that this lack of positive
effect at an earlier time point with higher dose
sheds doubt on the later time point. Our data
indicate, however, that duration rather than dose
appears to be the critical factor for
dystrophin production.

Although in an earlier study increased
dystrophin was observed in some patients by
week 12, the response was not consistent across all
patients. Study 201/202 showed increased
dystrophin in all biopsied patients at week 24 that
was sustained at later time points.

The week 180 biopsy is considered the most
important because samples were evaluated using methods, blinding, and controls developed in consultation with FDA. However, FDA noted concerns regarding the selection of the untreated controls, anatomical location of controls, and blinding procedures.

Baseline tissue was only available for 3 patients from study 201, therefore we obtained additional samples from a highly comparable group, untreated patients who were the first 6 patients with available tissue from the PROMOVI confirmatory study.

Of note, they had similar enrollment criteria to study 201 and were not previously analyzed for dystrophin. Collectively, this provided 9 untreated controls, which represent a robust internal comparator for measurement of dystrophin.

As the FDA noted, we compare biopsies from deltoid to biceps. There is no evidence to suggest that dystrophin levels would differ in these muscles since both are proximal upper extremity.
muscles equally affected in DMD patients. This was confirmed by our own analysis of the baseline samples.

Finally, these assays were performed by independent technicians who were blinded to sample treatment status with a different sample randomization used for each assay.

We have learned a lot about dystrophin measurement in the course of the eteplirsen development, and our methods have evolved accordingly. Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative.

This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is
Given these significant methodological differences, it is inappropriate to compare our data to literature approximations. Instead, treatment effect should be assessed by comparing untreated baseline tissue to post-treatment samples using the same validated assay. This enables accurate determination of a fold increase in dystrophin level.

Western blot analysis of week 180 biopsies show that 9 out of 11 biopsied eteplirsen patients in the 201/202 study had an obvious and quantifiable dystrophin band resulting in a mean of 0.9 percent. The untreated samples had a mean of 0.08 percent.

Importantly, this baseline calculation is based on a predefined protocol that was developed in collaboration with the FDA. This represents an 11.6-fold increase and includes the available baseline samples obtained from study 201.

The FDA questioned whether this robust increase in dystrophin level was significant based
on historical approximations in the range of 3 percent of normal. As detailed earlier, direct comparison cannot be made to literature values. The only scientifically valid comparison is to these untreated DMD controls.

Turning to our analysis of percent dystrophin positive fibers, FDA questioned certain important details, which I would like to clarify. First, only unenhanced images were used to score positive fibers. Second, an unbiased systematic sampling method was used to select the fields for image capture.

Third, a prespecified protocol was carefully developed to avoid overestimation of dystrophin positive fibers, with viewing conditions controlled to allow optimal viewing of the original unaltered images, positive fibers defined as having intensity above untreated DMD fibers in at least 30 percent of the membrane circumference, and a requirement that each pathologist be trained and pass prespecified qualifications prior to scoring.

The rigor of the protocol and training is
supported by the higher inter-rater reliability
that was observed for analysis of the week 180
images.

Three pathologists observed a significantly
higher mean percent dystrophin positive fiber count
and a 15.5-fold increase for eteplirsen patients in
comparison to untreated controls. The
immunohistochemistry images were also assessed for
fluorescence intensity by a computer algorithm.

As shown in this graph, a significant higher
mean relative fluorescence intensity and a 2.4-fold
increase was observed for eteplirsen patients in
comparison to the untreated controls.

As both Dr. Mercuri and I mentioned earlier,
DMD patients amenable to exon 44 skipping
experience a milder phenotype. The mean intensity
for eteplirsen is 22.6 percent, which is comparable
to the approximately 20 percent seen for exon 44
amenable patients.

In contrast to Western blot data, which
cannot be compared to published reports,
immunohistochemical intensity comparison is valid
when contemporary standardized methods are used.

Evaluating the relationship between Western blot and immunohistochemical intensity shows that, as expected, the normal controls are in the highest values. Untreated DMD samples are the lowest and week 180 treated DMD and Becker samples fall in between. It is important to note that one of the low expressing Becker patients overlaps with our week 180 treated samples.

A strong correlation between these two quantitative measures has been reported in several independent publications. As noted by the FDA, the correlation between Western blot and PDPF is not strong. This is not unexpected given that PDF is a semi-quantitative measure.

To summarize, we have clearly demonstrated that sustained production of de novo dystrophin by all measures employed. Biochemical evidence of functionality includes correct localization of dystrophin and key associated proteins to the sarcolemmal membrane. Taken together, these data clearly demonstrate that eteplirsen is working as
Next, I will present the clinical data that demonstrate that the observed increase in dystrophin results in a clinically meaningful benefit. Before I do that, I would first like to describe our early 48 week data and explain why it suggested the need for a longer study.

In an exploratory analysis, we looked at the first 48 weeks of study 201/202. We saw that 2 patients, shown in light blue, experienced rapid decline before the 24-week time point and lost ambulation shortly thereafter.

Based on what we know now, consistent increase in dystrophin is not observed until 24 weeks suggesting that these patients declined prior to dystrophin production. An analysis was conducted of continuously treated patients who remained ambulant, shown in dark blue, as well as the placebo delayed patients who rolled onto treatment at week 25, shown in gray. Both groups experienced relative stability.

Based on these limited but encouraging
results, study 202 was extended. To be clear, the two boys who lost ambulation remained on treatment and are included in all subsequent analyses presented.

In order to evaluate the long-term data from study 201/202, FDA suggested comparison to an external control group. This was accomplished by pooling eteplirsen data into a single group with the original placebo patients reset to time zero at the initiation of the eteplirsen treatment. This provides data from 12 patients for a 4-year time period.

A key aspect to the data comparison of course is the appropriateness of the external control. We recognize that a key issue for external controls is the potential for bias. We looked carefully at the regulations and guidance, and I would like to begin by addressing the key issues.

First, bias can be due to both known and unknown prognostic factors. We controlled for the key prognostic factors that are known.
Second, the selection of the control group should be made prior to the comparative analysis. We used prespecified selection criteria that were based on the 201 enrollment criteria.

Third, the disease course has to be predictable. We selected a homogeneous patient population with a predictable disease course.

Fourth, the endpoints need to be objective. We used a highly standardized 6-minute walk test measure.

Fifth, patient level data are required for comparison. We had 4-year longitudinal patient level data that was highly comparable on baseline characteristics, including steroid use and other standards of care.

Sixth, external controls are often perceived to have worse outcomes. I will show that the external control group was reflective of other natural history databases.

And finally, and most importantly, the treatment effect needs to be dramatic. You will see that this was certainly the case with
eteplirsen.

In partnership with leading DMD experts, Sarepta actively searched for a natural history data. Twelve databases were identified having extensive clinical data, however only two had 6-minute walk test data beyond baseline available for analysis. Of note, the CINRG database did not have long-term 6-minute walk test data at that time.

The two databases identified were the Italian DMD Telethon and the Leuven Neuromuscular Research Center in Belgium. The studies began enrolling patients in 2007/2008 and have continued in a time period that is contemporary with study 201/202. Both databases had longitudinal 6-minute walk test data available, but only the Italian registry had the NSAA data available as well.

Importantly, all patients attending a participating clinic who met eligibility criteria were enrolled in the studies. Results from these investigator initiated studies have been published in peer review journals.
All centers in the studies were treating patients according to the international standards of care for DMD that were discussed by Dr. Mercuri. FDA raised concerns about lower adherence to standards of care for children in Italy, however, this is of limited relevance to the actual care received by our external control patients who were seen at neuromuscular specialty clinics. As I will later demonstrate, our external control had extremely high compliance to the standards of care.

As is common in rare diseases, treating clinicians represent a small but highly collaborative international community. Importantly, the 6-minute walk test was assessed by the same method for eteplirsen patients and for external controls.

Both databases as well as the eteplirsen study used the modified 6-minute walk test protocol adapted for use in DMD. As was described by Dr. Mercuri, this included use of the same scripted encouragement. In addition, the lead physical therapist for the Italian registry and study
201/202 previously worked together on an international effort to standardize the protocol and training for the 6-minute walk test in DMD. This ensured comparable clinical evaluations between the various sites.

Having obtained the patient level data, we next set out to find the most appropriate patients for comparison. The enrollment criteria for study 201/202 were used to select patients from the external control group. These included steroid use, age greater than or equal to 7 years, and a mutation amenable to exon 51 skipping. Importantly, these filters were defined before data analysis began.

I would like to remind you that these criteria were specifically designed to select for boys in the decline phase of the disease.

Pooling the data that Sarepta received from the two databases rendered a raw data set of 186 patients. The Italian Telethon only provided patients who had been evaluated for at least 3 years, while the Leuven Neuromuscular Research
Center provided patients who had been evaluated for varying lengths of time. The selection criteria from 201/202, just described, were applied to these patients.

An initial filter was applied requiring steroid use at baseline as well as a minimum of both a baseline and one post-baseline 6-minute walk test result. A second filter was applied to exclude patients younger than 7 who were likely to be improving in the 6-minute walk test due to growth and maturation.

Since mutation type impacts disease severity, filters were applied to find patients amenable to skipping any exon, and finally amenable only to exon 51 skipping. Efficacy results will compare eteplirsen patients to this primary analysis group.

In addition, a secondary more conservative comparison to a larger population of 50 patients amenable to any exon skipping included milder exon 44 patients was presented in our briefing document.
A critical question is how comparable this external control group is to the eteplirsen group. We see here that the eteplirsen cohort on the left is highly comparable on key prognostic factors to the primary external control group on the right. Looking first at the mean baseline age, we see that the groups are very similar.

Mean baseline 6-minute walk test values are also highly comparable with the groups differing by less than 10 meters. Of note, all deletion mutations observed among the 12 eteplirsen boys are also represented in the external control.

As Dr. Mercuri detailed, steroid use has been shown to impact disease progression. Importantly, the eteplirsen patients as well as all external controls were on a stable dose of steroids at least 6 months prior to enrollment and remained on steroids throughout the study.

The two most commonly described steroids in DMD, deflazacort and prednisone, were used in equal proportion by both groups. Of note, the majority of patients in the external control actually
maintained a higher dose than the eteplirsen patients.

As FDA noted, there are two minor differences in steroid treatment between the external control and eteplirsen, neither of which significantly impacted the 6-minute walk endpoint.

First, the mean age of steroid initiation for external control is approximately 1 year older than eteplirsen. This difference is partly attributed to a single external control patient who began steroid use at age 10.7 years. Of note, he had a better prognosis and maintained ambulation until he was over 15.

Second, a lower percentage of eteplirsen boys received an intermittent steroid regimen in comparison to external control. Sensitivity analyses for both of these variables demonstrate minimal impact on the primary endpoint.

In addition, we plotted the change in 6-minute walk test by steroid regimen for the external control. The intermittent patients shown in orange experienced similar declines as the
continuous patients shown in green. Taken together, with a sensitivity analysis, this suggests that steroid dosing frequency did not affect the results of the 6-minute walk test in our analysis.

Physical therapy and use of orthoses can also impact ambulation. As shown here, the external control patients received a higher level of physical therapy intervention with all 13 meeting with a physical therapist at least twice a week.

Additionally, there was a high compliance with the use of night splints. This demonstrates that the external control patients had high adherence to standards of care. This is not surprising since they were treated in leading neuromuscular centers.

In addition to looking at comparability of baseline characteristic, it is important to address concerns regarding the potential for motivational bias in the external control. FDA had performed an alternative comparison for eteplirsen based on the
To test for the potential motivation bias, we did an analysis comparing the 6-minute walk test results for our external control group to this data. Patients in the drisapersen study were also amenable to exon skipping and on steroids. However, they included patients younger than 7 who, as Dr. Mercuri noted, would be expected to improve over time.

These drisapersen patients were initially on placebo, shown in dashed black, and then rolled over onto treatment, shown in solid black. Motivation does not appear to be a factor given that our external control, shown in yellow, experienced similar declines to patients in the drisapersen trial.

I would now like to clarify a few misunderstandings regarding our key data and then review the clinical results. As it relates to the external control, FDA raised three key issues.

First, there was a concern that revisions occurred to the external control data regarding
continuous versus intermittent steroid use. To clarify, 3 patients with unknown regimens at the time of NDA submission were later reported by the investigator as receiving a continuous regimen.

Second, the FDA stated that 2 patients left to enter interventional trials, leading to potential difference between eteplirsen and external control patients. In fact, we acquired the missing 6-minute walk test data for these two patients after they participated in the placebo arm of an interventional study and have included their 6-minute walk test results in the analyses.

Third, as Dr. Mercuri noted, it is common for patients to have a 6-minute walk test of zero while still being able to perform the 10-meter walk run.

In addition, FDA raised two key concerns in the approach to Sarepta's analysis of the 6-minute walk test and the North Star ambulatory assessment. First, they noted that eteplirsen patients had two opportunities to perform a functional test whereas natural history patients had only one. To be
clear, day 1 values for the 6-minute walk test and all other measures were compared to single external control measurement.

Finally, we would like to clarify that while FDA identified 2 external control patients as having missing North Star ambulatory assessment values, we correctly incorporated these values into our analysis and did not assign them values of zero. You can see that we have carefully reviewed the data, and we will be happy to address any other questions.

Comparison to the external control to eteplirsen was conducted over 3 to 4 years. Four years of data were analyzed for 6-minute walk test and loss of ambulation, while 3 years of data were analyzed for the North Star ambulatory assessment and ability to rise. These time periods were based on the availability of external control data.

As I review the results, keep in mind that the treatment expectation for eteplirsen is to delay but not necessarily to stop disease progression. Any preservation of ambulation, even
by a couple of years, would significantly impact
the lives of patients and their families.

Our primary analysis is comparison of the
external control group to eteplirsen patients on
change in the 6-minute walk test. In this
analysis, any patient who lost ambulation
contributed a score of zero to the mean.

As you can see the two groups had highly
comparable 6-minute walk test values at baseline
and year 1, confirming their similarity. We did
not expect an immediate separation between treated
and untreated patients because, first, an increase
in dystrophin expression is not observed until
24 weeks. And second, time is required for the
untreated control group to decline.

After year 1, the groups diverge, and by
years 3 and 4, we see a nominally significant
difference of 148 and 162 meters, demonstrating
that eteplirsen slowed disease progression. This
large magnitude of effect is equal to the length of
nearly two football fields.

In this graph, individual 6-minute walk test
results are shown in yellow for the exon 51 external controls. These patients experienced declines in 6-minute walk test over 4 years, and 10 lost ambulation by year 4, as indicated by a 6-minute walk test score of zero.

In comparison, the eteplirsen group, shown in blue, declined more slowly after year 1. No additional patients lost ambulation after year 1. As you can see, the difference is not driven by a few patients who performed particularly well or a few external control patients who performed particularly poorly.

For our analysis, loss of functional ambulation is defined as the inability to execute the 6-minute walk test. This bar graph shows the estimated loss of ambulation at annual time points based on Kaplan-Meier analysis. Two external control patients had missing data, and Kaplan-Meier analysis properly accounts for this.

The cumulative loss of ambulation over the first 4 years remain constant at 17 percent for eteplirsen patients. In contrast, a continual
increase in loss of ambulation is observed in the external control patients culminating in an 85 percent probability of losing ambulation by year 4.

FDA presented the loss of ambulation by age. The analysis shown here is from the CINRG database, a global, multicenter study of DMD. These are steroid treated patients amenable to exon 51 skipping similar to eteplirsen and external control patients, however, there are two important differences when comparing the CINRG data to eteplirsen.

First, the definition of loss of ambulation for CINRG was full wheelchair use and was confirmed by inability to perform the 10-meter walk/run when possible. This is critically different from our definition, which was zero on the 6-minute walk test.

As mentioned earlier, it is not unusual to see a zero on the 6-minute walk test and still have a positive value on the 10-meter walk/run. Because of these different definitions, the CINRG database
is more likely to report a later loss of ambulation in some patients. Despite this, our external control, shown in dashed yellow, performed somewhat better than these CINRG patients.

The eteplirsen patients shown in blue appear to behave differently than either the CINRG or the external control groups. Of note, the eligibility criteria used for eteplirsen has an upper limit of 440 meters on baseline 6-minute walk test, which precludes milder patients who are likely to walk longer. However, these milder patients were not excluded from the CINRG database.

FDA focuses on the outliers from the CINRG database to suggest DMD patients maintain ambulation into their late teens, concluding that eteplirsen boys do not differ from the natural history. Of note in the CINRG database, there are only 3 boys who are walking past the age of 15.

The more appropriate comparison is the median loss of ambulation between these three groups. The median ages of loss of ambulation are 12 for CINRG, 12.9 for the external control, and
the median loss of ambulation has not yet been reached for eteplirsen boys. Most importantly, eteplirsen preserves ambulation longer than either the CINRG database or the external control.

We are fortunate to have Dr. Craig McDonald, the chair of the CINRG study, available today to answer questions regarding the database and loss of ambulation in DMD.

In addition to ambulatory ability, a number of supportive endpoints were also evaluated. Comparison to external control for these endpoints is shown through year 3. Similar to the 6-minute walk test results, the North Star ambulatory assessment shows a slower decline in the treated group at 2 and 3 years following the same trend as the 6-minute walk test. While the observed difference of 2.4 points on the North Star ambulatory assessment is not significant, it represents the critical preservation of one or more activities of daily living.

Here we show the ability to independently rise from supine for external controls compared to
eteplirsen patients. Ability to rise is a more standardized definition since in contrast to rise time, it does not allow for external support. Consistent with the 6-minute walk test results, the two groups are initially comparable and then diverge.

By year 3, more than half of the eteplirsen patients could still rise from the floor independently compared to only 8 percent of external control, a difference that is nominally significant.

In summary, it is our position that the data you have seen confirm eteplirsen's mechanism of action and demonstrate that eteplirsen slows disease progression. Eteplirsen is the first therapeutic to unequivocally demonstrate an increase in dystrophin following treatment.

The external control is a highly comparable and appropriate comparator to evaluate eteplirsen's clinical effect. Analysis of drisapersen placebo and CINRG data confirm that our external control is representative of natural history.
Eteplirsen slowed disease progression, demonstrating a clinically meaningful effect on the 6-minute walk test and a dramatic difference in loss of ambulation. Eteplirsen benefit is further supported by the North Star ambulatory assessment and ability to rise from supine.

While we demonstrated clinical benefit in our initial studies, because we are seeking accelerated approval, confirmatory studies are required for full approval. When we had to make the critical decision of how to further evaluate eteplirsen, we determined that a placebo-controlled trial would not be feasible because there were not enough eligible exon 51 amenable patients due to other ongoing trials. In addition, the patient community expressed opposition to a long-term placebo-controlled eteplirsen study.

Therefore, in consultation with FDA, a flexible approach was adopted using non-exon 51 amenable patients to a comparator arm. This approach incorporated what we learned, including the need for a longer study duration and updated
enrollment criteria to exclude rapidly progressing boys such as the two who lost ambulation in study 201.

The first confirmatory study is an open-label comparison of exon 51 patients treated with eteplirsen to untreated DMD patients who are amenable to skipping other exons but who would not benefit from eteplirsen.

The second study is a double blind, placebo-controlled trial of two follow-on drugs. Both have the same PMO backbone as eteplirsen and utilize the same mechanism of action, but rather than skipping exon 51 these drugs skip exons 45 and 53, respectively.

To provide further detail, the first confirmatory study, PROMOVI, is a 96-week open-label, multicenter study comparing 60 eteplirsen patients to 60 untreated, non-exon 51 amenable boys having the same entry criteria.

These criteria are similar to study 201/202 but with updated 6-minute walk test cutoffs to exclude patients likely to decline before
dystrophin can be produced. This study is already underway, but a data readout is not expected for at least another 2 to 3 years.

The second study, ESSENCE, is a 96-week randomized, double-blind, placebo-controlled multicenter study of our next two drugs, which treat patients amenable to skipping exon 45 and 53, respectively.

Recall from Dr. Mercuri's presentation that patients amenable to skipping exon 45 or 53 experienced a similar rate of decline on the 6-minute walk test as patients amenable to skipping exon 51. This will be a 99-patient study with a 2 to 1 randomization of drug to placebo with entry criteria matching PROMOVI. Enrollment is expected soon.

I would now like to introduce Dr. Eliopoulos who will review the safety data.

Applicant Presentation – Helen Eliopoulos

DR. ELIOPOULOS: Thank you, Dr. Kaye.

Good morning. Following a brief description of non-clinical data, I will present the integrated
analysis of safety, including adverse events that were common, serious or severe, resulted in discontinuation, or were of special interest.

Eteplirsen is a PMO structurally and biologically distinct from other RNA analogues. In non-clinical studies of eteplirsen, the kidney was identified as the organ of toxicity. In contrast to other RNA analogues, including one recently reviewed by this committee, toxicities such as immune activation, thrombocytopenia, coagulopathy, or vasculitis were not seen with eteplirsen.

The integrated safety analysis includes 114 DMD patients from 7 studies, all patients with mutations specifically amenable to exon 51 skipping. Twenty-six patients received lower eteplirsen doses and were from study 33, which administered a single IM dose or study 28, dose ranging for IV eteplirsen.

Eighty-eight boys received the proposed dose of 30 milligrams per kilogram or higher, including 12 boys from pivotal studies 201/202, who have received eteplirsen for about 4 years. Younger
patients, age 4 to 6 from study 203, as well as
patients with more advanced DMD from study 204,
have contributed to the integrated set.

This table lists common adverse events
occurring in 10 percent or more of the 114
patients. The majority of events were mild and
transient, resolving with continued eteplirsen.
And as you could see, many of these could be
anticipated in a pediatric population with
Duchenne.

Only 2 of 114 patients had serious adverse
events, but neither of these appear drug related.
One patient, an 11-year-old boy, had a femur
fracture after falling out of his wheelchair. He
had previous events of severe but non-serious
balance disorder and bone pain. And the second, a
9-year-old boy, had post-operative vomiting after
general anesthesia. Of note, there have been no
fatal or life-threatening events with eteplirsen.

Out of 114 patients, there was only 1 who
discontinued eteplirsen due to adverse events, and
this was a 10-year-old boy who was reported to have
cardiomyopathy after 7 weeks of a low dose of eteplirsen at 4 milligrams per kilogram. This was based on an observed decrease of left ventricular fractional shortening on echo. The investigator considered this as severe and possibly related to drug.

To further evaluate, Sarepta undertook an independent cardiology review, which interpreted the echo findings as normal and considered that changes in fractional shortening were possibly due to technical factors.

There was one additional case of cardiomyopathy in the integrated set, not leading to study drug discontinuation, in a patient with preexisting history. Overall, these two reports represent a rate of about 2 percent consistent with the known prevalence of cardiomyopathy in DMD.

Severe events were experienced by three additional patients. A 7-year-old boy experienced bleeding from a Portacath incision site after swimming. Coagulation parameters were normal at the time of the event.
In two other patients, events of nasal congestion, hemorrhoids, and back pain due to a fall were reported, and again, these appeared consistent with events that may occur in a pediatric DMD population.

Adverse events of special interest were based on the non-clinical findings for eteplirsen as well as events of interest from the clinical experience with other RNA analogues.

As non-clinical studies identified the potential for kidney toxicity, a broad review of renal events was conducted. There were 11 patients with proteinuria described as protein detected by dipstick based on urinalysis. All events were mild and transient. There was one patient with adverse events of increased BUN and creatinine in the setting of dehydration occurring at week 88 of eteplirsen. These resolved by the time of retest 11 days later and have not recurred with continued eteplirsen for a period of over 2 years.

As immunogenicity has been an issue for other RNA analogues, potential infusion reactions
have been reviewed. A subset of 107 patients have received IV eteplirsen, representing over 3900 infusions. Twenty-two percent of these patients experienced an infusion site event, this table listing those occurring in 2 or more patients.

Most events were described as catheter or infusion site pain or hematoma consistent with placement of a catheter device. Of note, there were 4 events of mild pyrexia considered unrelated to drug. An additional report of mild temperature elevation occurred coincident with an eteplirsen infusion and is therefore considered a potential adverse drug reaction. There have been no serious or severe infusion site reactions with eteplirsen.

In the all-eteplirsen group, 24 percent of patients had events, which were assessed for potential hyper-sensitivity. All events were non-serious and resolved. The majority, including rash and pruritus, were mild and considered unrelated to study treatment by nature of the temporal relationship or lack of recurrence with ongoing treatment.
Two types of events, mild erythema, and flushing, occurred during eteplirsen infusions. They were considered related by the investigators and represent potential mild adverse drug reactions. There have been no serious or severe events related to hypersensitivity with eteplirsen.

Review of the safety database and longitudinal laboratory data identified no clinically significant events for thrombocytopenia, coagulopathy, vasculitis, immune-mediated disorders, or hepatic toxicity, consistent with the absence of such findings in non-clinical studies of eteplirsen.

In summary, characterization of the eteplirsen safety profile is early, however, no significant safety risks have been identified. The majority of reported adverse events have been mild and resolved with continued therapy, suggesting they were not drug related.

Favorable tolerability is demonstrated by the low rate of discontinuations and serious events. Sarepta continues to evaluate the safety
of eteplirsen through monitoring of ongoing trials, as well as planned post-marketing surveillance and a DMD registry.

I would now like to introduce Dr. Mendell, the principle investigator for study 201/202, who will provide the clinical perspective for eteplirsen in the treatment of boys with DMD.

**Applicant Presentation – Jerry Mendell**

DR. MENDELL: My name is Dr. Jerry Mendell, and I currently serve as director of the Center for Gene Therapy at Nationwide Children's Hospital. I'm uniquely positioned to provide a clinical perspective as the PI for the eteplirsen 201 and 202 studies since 2011. I'm a paid consultant for Sarepta in preparation for today, but I stand to gain no financial benefit from FDA approval of eteplirsen.

My experience in the management and care of DMD boys extends back to my post-doctoral position at NIH in 1969. When I started caring for DMD boys at that time, there were no treatments, and I made a personal commitment that over my lifetime, I
would make a difference for boys with this devastating disease.

There are three elements that emphasize the foundation for eteplirsen approval for the treatment of DMD. I refer to these as the treatment triad.

The first leg of the triad is prolonged ambulation. To be clear, the FDA is suggesting that boys with DMD are able to walk until the age of 16. This is not my experience, nor is it reflected in the data from CINRG, which shows loss of ambulation at a median age of 12 in exon 51 amenable patients. In the eteplirsen study, 10 boys are still walking 4 years after starting therapy. Their median age is 13.4, and the median age of loss of ambulation has not been reached for this cohort.

Why is this important? Simply put, the complications of wheelchair dependency have a major cascading effect that is both physical, including scoliosis and osteoporosis, and emotional, a change in body image leading to a loss of self-esteem. In
addition, many of the rapidly advancing translational treatments are denied to wheelchair-dependent patients.

The second leg of the triad is the safety profile of eteplirsen. I have done many clinical trials over the past 40 plus years, and I have never seen tolerability like we have seen in this trial. There has not been a single serious adverse event related to treatment in over 3900 infusions of eteplirsen.

The third leg is what I refer to as the consistency profile of eteplirsen treatment. This is best illustrated by the maintenance of ambulation after 4 years of therapy.

Dr. Kaye presented an exploratory analysis excluding the two boys who lost ambulation early in the study. Here we see the mean change from baseline through week 216. For clarity, we have shown both treatment groups starting at the zero point.

What interests me is what happens after week 48. Here we see a long-term stabilization and
a consistent parallel course between both groups, however the placebo delayed treatment group never catches up, sending a clear message that there is a treatment effect of eteplirsen. The consistency of the data is remarkable giving the protocol mandates that the distance measured for each patient be recorded and transcribed in the case report forms without looking back at the previous result.

I'd also like you to know that what we have observed in the eteplirsen treated patients is very different from what I have seen in the natural history. I know this because every DMD boy who comes to Nationwide Children's Hospital for ongoing care undergoes a 6-minute walk test with the same physical therapist, under the same condition as the eteplirsen trial, and we simply don't see similar results.

This graph also emphasizes that there are no claims that eteplirsen is a cure for DMD. Eteplirsen slows progression, which results in maintained ambulation.

The next slide allows us to look again at
loss of ambulation over 4 years. In the exon 51 external control matched for age and mutation, the risk of loss of ambulation is 85 percent for external control patients compared to 17 percent for eteplirsen.

As previously stated, a major goal of this trial was to delay the loss of ambulation. Our data suggests that the unequivocal increase in dystrophin by eteplirsen cannot be ignored as an explanation for prolonged ambulation. Preserving walking is key to maintaining physical and emotional wellbeing.

The numbers are one thing, but my personal enthusiasm for these findings is best demonstrated by the quality of walking in eteplirsen treated patients, as we see on the next slide.

This is Billy in the red cap. He's now 15, and he's one of my patients in the eteplirsen trial. Here he's walking in the last mile of the Pittsburgh marathon. First of all, boys at this age with DMD usually don't walk, and they certainly don't walk in the last leg of a marathon. But here
he is, and I want you to watch closely because not only does he walk, but he has gained enough self-esteem to attempt jogging as if to emulate other participants in this highly competitive trial. Go Billy.

(Applause.)

This quality of ambulation at 15 just doesn't happen in DMD.

In summary, I see treatment of DMD as a race against time. If you shadowed me in clinic, you would find that most boys at age 14 are in a wheelchair. Fifteen-year-old boys like Billy don't maintain ambulation by accident. This is a very gratifying result for a long-term clinician.

Eteplirsen offers a genuine opportunity to change the natural history of this disease by slowing progression and improving quality of life. I can't see any grounds for withholding this drug for DMD boys. The opportunity before the panel is to give the DMD boys in my clinic, and in other clinics, the same chance as we observed in the eteplirsen trial.
I want to thank this panel of reviewers, the team of researchers at Nationwide Children's Hospital, and the collaborators at multiple sites for helping to make this happen. Most of all, I want to thank the 12 heroic boys and their families who selflessly dedicated themselves to this groundbreaking research. And finally, I want to turn this podium back over to Dr. Kaye for concluding remarks.

(Applause.)

**Applicant Presentation – Edward Kaye**

DR. KAYE: Today the FDA has presented to you a number of important questions for your consideration. To help you in your deliberations, allow me to conclude by reviewing three of the most critical and then offer Sarepta's position on each.

The first question focuses on the provision of adequate evidence. The agency has asked if eteplirsen produces dystrophin to a level that is reasonably likely to predict clinical benefit. Today we presented data that shows an unequivocal increase in functional de novo dystrophin by three
complementary methods. Most important, we shared
with you the fact that even small amounts of
dystrophin are known to confer clinical benefit.

The second question focuses on the 6-minute
walk test. It asks if the test is sufficiently
objective and free of bias to allow for a valid
comparison. Sarepta's position is clear. The
6-minute walk test is both standardized and
considered highly reliable. Moreover, our external
control results are consistent with other natural
history databases.

The third and final question focuses on
whether our clinical studies have provided
substantial evidence that eteplirsen is effective
for the treatment of DMD. Once again, our answer
is yes. The data set we've presented to you shows
a dramatic positive effect on the 6-minute walk
test as well as on the loss of ambulation for over
4 years.

All of us here today agree that bringing new
and effective therapies to boys suffering from DMD
is both critical and urgent. But we also know that
in the field of rare diseases large placebo-controlled studies present significant challenges.

As Ms. Ruff said in her opening remarks, given the limitations of our database, we both understand and appreciate the difficulty of your decision today, yet we believe it is both reasonable and prudent to approve eteplirsen based on the totality of the data we have presented today.

Let me conclude our formal presentation with this. Sarepta stands ready to work with the entire DMD community, patients, caregivers, providers, and our colleagues at the FDA to continue our groundbreaking work and hasten the day when we can say with certainty we have a cure.

I would now like to introduce Christine McSherry from the Jett Foundation.

(Appplause.)

**Applicant Guest Speaker Presentation**

**Christine McSherry**

MS. McSHERRY: Thank you, Dr. Kaye, and to
Sarepta for donating some of your time today for our presentation. I am Christine McSherry, a registered nurse, the executive director at Jett Foundation, but most importantly a mom of a 20-year-old with Duchenne.

My son, Jett, is enrolled in study 204, Sarepta's safety study for the advanced patient population, and he's been receiving eteplirsen for 18 months. Jett took his last step when he was 13.

I started the Foundation in 2001 with a mission to improve the lives of those affected by Duchenne. The Foundation does not have any financial interest in the outcome of this meeting, and has not been compensated for this project.

As you heard from the sponsor's presentation, FDASIA gives patients a voice in the drug development process. With this law in mind, we met with CDER officials many times over the last 4 years.

It was never our intent for the results of the videos to be part of this outcome. It was simply intended to bring context and perspective to
FDA on outcomes that are meaningful to patients.

In the spring of 2012, prior to the release of public data, we heard stories about boys doing well on eteplirsen. There were small but meaningful things that they had never done prior to taking the drug, like opening bottles of water and bags of chips. Boys with Duchenne often struggle with these types of activities.

In April 2013, we met with CDER to discuss the patient experiences that we heard about and they asked us for video evidence. In June, we returned and presented videos of boys who were jumping into pools, walking their dog, and participating in sports.

CDER officials asked us to quantify outcomes important to patients, so as requested, in July of 2015, we presented and submitted data on activities of daily living, or ADLs, to FDA. At this meeting, they indicated these results would be included in the review of the eteplirsen NDA.

We collected this information through semi-structured videotaped interviews that included
rating scales. Many themes emerged in this data, but due to our limited time today, I'll only be sharing 4 key findings: spontaneous falls, walking after fractures, fatigue, and ADLs.

Through social media requests, 8 of the 12 participants in study 202 agreed to be interviewed. All of these boys were over the age of 7 and in the decline phase of ambulation. And importantly, we interviewed the 3 largest decliners in the study, including the 2 patients who lost ambulation early and a boy who broke his tibia.

These interviews took place after the boys had been receiving therapy for 3 years. We also interviewed 3 boys from study 204. In total, 11 boys participated.

Our research led to several key findings, all things that we would never expect to see in the normal progression of Duchenne. The first finding was a decrease in spontaneous falls. Now, let's take a look at a video of what a typical fall looks like for a child with Duchenne. This video was taken during a 6-minute walk test.
Now, watch carefully. We've all tripped. This boy doesn't trip. As you're watching, look at his feet very carefully. He doesn't trip. His quads just give out, giving him no time or warning to brace his fall.

(Video played.)

MS. McSHERRY: That is a Duchenne fall. In this instance, the physical therapist is there to pick the boy up off the floor. By the age of 9, the majority of boys with Duchenne are losing the ability to get off the floor themselves. So if this happens when no one is around, the only alternative is to lie and wait until someone comes to find him. Boys of this age are typically gaining independence. In contrast, these boys can no longer be left alone.

Now, let's listen to how one boy describes his experience falling prior to taking eteplirsen and then after he's been on therapy.

(Video played.)

MS. McSHERRY: "I don't even remember when I collapsed the last time." Daily diary, spontaneous
falls. So the mother of this patient kept a daily
diary of his spontaneous falls. The Y-axis
represents the number of spontaneous falls per day,
while the X-axis represents time. This boy started
on drug in November of 2014, and he was falling
twice a day, and the falls decreased until March of
2015 when his falls stopped. And without the fear
of falling, he's able to play soccer, his favorite
activity, for an extended period of time.

We asked caregivers to report the number of
daily falls from the beginning of the trial to the
time of our interview. The bars on the X-axis
represent the patients from study 202 at baseline
and 3 years later. The Y-axis represents the
number of falls they experienced at those two time
points.

The gray bars in the red circle represent
the boys, 2 boys, who lost ambulation early in the
trial, and as you can see, they experienced over
4 spontaneous falls a day prior to losing
ambulation.

The red arrows highlight 4 boys who had been
falling anywhere between 5 times a day to twice a week. The yellow bars reveal that over time, they all essentially stopped collapsing. And surprisingly, the red arrows signify that no ambulatory boy is falling 3 years after starting drug. This just doesn't happen with boys who have Duchenne at this stage in their disease.

Walking after fracture, key finding number 2. Spontaneous falls are also devastating because they can lead to fractures, which typically marks the end of our sons' walking. Families affected by Duchenne have the same fear that you would have of an elderly parent falling and breaking a hip.

During our interviews, a highly experienced physical therapist, who specializes in Duchenne, told us, quote, "If you're 10, 11, or 12 and you break a leg, I'm shocked if you would ever walk again. I would say 9 times out of 10, that's the end of your walking."

Boys with Duchenne are at high risk of a fracture due to corticosteroid use. We learned
that 4 boys on eteplirsen had fractures, yet all 4 regained the ability to walk. For boys their age, it's not what we would expect. We would expect them to never walk again.

Key finding number 3, Duchenne related fatigue. It's important to understand this distinction. Because of Duchenne, these boys reach the point of exhaustion much faster. As the disease advances, they often can't make it through a full day of school. They crash, sleeping for hours.

However 5 of the 8 boys taking eteplirsen either decreased or maintained their level of fatigue. This is not what we would expect over 3 years. The other 3 boys were the ones who either lost ambulation or experienced a fracture.

As I said before, I'm a mom of a 20-year-old boy with Duchenne. And as the disease progresses, these boys are completely exhausted and lose the ability to do everyday things. The simple task, such as lifting a spoon to their mouth, feels like they're lifting heavy weights for them. And simple
tasks, like scratching your nose or turning over in bed, become impossible.

   Earlier in the disease when boys tire, it leads them to use a wheelchair more often. Let's listen to one boy's experience after being on eteplirsen.

   (Video played.)

   MS. McSHERRY: Maintaining the ability to walk, something we take for granted, but this boy is able to walk with his friends. He can walk his dog, and he can play like a normal kid.

   The loss of ambulation changes every aspect of normal daily living, from accessing a friend's house, to taking family vacations, to home modifications. It's just endless. Remember, ambulation isn't just about walking. It also benefits bone health, prevents scoliosis, and supports breathing. It touches not just the boy, but everyone else.

   For the boy that we just heard from, the 6-minute walk test tells a story, but not the whole story. For example, while this boy's 6-minute walk
test remains stable, it didn't capture the improvements that we saw. He stopped falling, and his fatigue was reduced. Just looking at the 6-minute walk test you wouldn't see the improvements in these other important outcome measures.

Key finding number 4, participating in life for ADLs. Typically, when boys lose ambulation, they quickly lose upper arm strength. And we fully understand that eteplirsen is not a cure, and it only slows the progression of the disease. So it was important for us to see if the drug was having a benefit in the non-ambulatory boys.

For this reason, we looked at the twin boys who lost ambulation. We assessed 8 activities of daily living that don't involve walking, such as using a computer, feeding oneself, brushing teeth, and using a cell phone. Despite coming off their feet, both boys have maintained the ability to do these activities over the 3-year time frame. This would suggest a benefit in the non-ambulant population.
The collective experience tells us that eteplirsen is having a real and concrete impact on the rate of disease progression. For the boys that we interviewed, who were all between the ages of 10 and 13 and on drug for over 3 years, we saw a decrease in spontaneous falls, the ability to walk after a fracture, and the stabilization or improvement in fatigue, and the maintenance of ADLs in the non-ambulatory boys. In the time that it will take to complete the confirmatory study, many boys in our community will either lose the ability to walk, to lift their arms, or to breathe.

Just two short weeks ago, Dr. Janet Woodcock spoke at a breakthrough therapy briefing on Capitol Hill by Friends of Cancer Research. She spoke about type 1 errors, false positives, and type 2 errors, false negatives.

In the context of FDA, a type 1 error would be risk of approving drugs that are unsafe or ineffective, whereas a type 2 error is not approving a drug that is safe and effective. She said that type 2 errors are not talked about enough.
and there needs to be a balance between the risk of committing a type 1 versus a type 2 error.

This afternoon when you hear the human side of this story, from those who have benefited from this drug as well as others waiting for treatment, I hope you keep in mind type 2 errors and recognize that there is a very real human cost to making a conclusion that a drug doesn't work when it really does. Thank you.

(Applause.)

DR. ALEXANDER: Thank you. Thank you for the presentation.

(Applause.)

Clarifying Questions

DR. ALEXANDER: Thank you very much. If everyone could please take their seats.

Thank you. We'll now proceed with clarifying questions to Sarepta Therapeutics. Are there any clarifying questions? Please remember that all participants from the panel, FDA, and Sarepta should state their name for the record before you speak. If you can, please direct
questions to a specific presenter.

   Dr. Hoffman?

   DR. HOFFMAN: Richard Hoffman. Eteplirsen looks to be a very promising disease-modifying agent, and I was wondering if the sponsor had any plans to do a larger study in younger boys and at a much higher dose. Thank you.

   MS. RUFF: I'd like to ask Dr. Kaye to come to the podium.

   DR. KAYE: So the answer to your first question is, yes, we have a large 60-treated patient open-label study that is ongoing, and we have another study in our -- which will be a double-blind, placebo-controlled study, that will be 99 patients in the 2 to 1 randomization for the next two drugs. So that was the way of being able to do a double-blind, placebo-controlled.

   Our dose that we had determined is 30 milligrams per kilogram, and this was based on the pharmacodynamic effect. We didn't see any difference. However, we do plan to continue to look. We're looking at -- we have a study right
now in younger patient populations, and we have a study in older populations. And we have plans to go down to the newborn level, and we will be looking at a number of different ways of dosing, even at younger ages.

DR. ALEXANDER: Thank you. Dr. Onyike?

DR. ONYIKE: So I'm not exactly sure who I'm directing this to, so please, Dr. Kaye or someone else with the technical qualifications should take the question. What I really want to understand is about the mean relative fluorescence intensity. I'm having difficulty understanding how it's a quantitative measure because you're essentially -- it seems to me you have pathologists looking at slides and trying to make decisions about the intensity of a dye relative to what scale is very unclear.

But I can imagine that with the naked eye, it's very hard to achieve very graded quantification of staining unless you have some sort of spectrum that you make a reference to, which I don't think you have.
So explain how exactly we should take the mean relative fluorescence intensity as seriously as say, the Western blot, in terms of quantification?

MS. RUFF: So to address your question about quantification using intensity, I'd like Dr. Frank to come to the podium.

DR. FRANK: Thank you. My name is Diane Frank. I'm the senior director of translational research at Sarepta. The intensity measures were made using a computer algorithm, because as you correctly stated, the human eye is not very good at measuring intensity levels with the resolution that the computer program's able to do. Because a computer program has a definition to look at the pixel intensities in the region of the membrane, it can calculate the average intensity pixel by pixel across the image.

DR. ONYIKE: If I may follow on, how do you translate then these intensities into actual tissue concentrations at the sarcolemma?

DR. FRANK: So one of the challenges in the
field is there is no absolute standard for
dystrophin, therefore, we have no ability to do an
absolute dystrophin concentration, such as a
microgram per square centimeter.

As a result, we make our comparisons to one
consistent normal control, and that's why you're
seeing percent normal. And then the change of our
therapeutic effect is a relative change due to the
lack of an absolute standard, so that we're looking
at the change from baseline.

DR. ALEXANDER: Thank you. Dr. Green?

DR. GREEN: Yes, I wanted to know whether
there was any specific language that was included
or excluded before the 6-minute walking test in
both subjects and the controls.

MS. RUFF: If I can just clarify. Are you
talking about the script for the 6-minute walk
test?

DR. GREEN: Well, I'm talking about -- no,
I'm actually talking more about in advance in
preparation for the 6-minute walking test, and not
only in those who had it administered as part of
MS. RUFF: So I'd like Dr. Mendell to talk about the eteplirsen boys, and then Dr. Mercuri to talk about the external control boys.

DR. MENDELL: Well, the 6-minute walk test is done in a standard fashion. The boys are explained the test prior to it being done. And then during the trial, they, one, are told that they must walk and not run, and they should try as hard as they can. And there is encouragement for them to continue the walk as long as they can.

If they fall, there is someone behind them to, as you saw in the video, help them get up and then continue to walk. For those boys who can't continue because they have been injured or in pain or whatever, then they will stop, and that will be the end of the walk test.

But it's done in a standardized fashion. The same therapist does the same test on every single patient, and it's the same thing for our clinic when the boys come, even outside of the study.
DR. ALEXANDER: Can you speak into the microphone please, Dr. Green?

DR. GREEN: And there are no family members present during this?

DR. MENDELL: There are absolutely no family members present when the boys are tested.

DR. MERCURI: The same applies for the external controls. There is a manual. There are strict instructions on how to perform it. It's the same way we perform it in clinical routine and in the clinical trials. And the instructions are very strict also on the time of the encouragement and so on.

So these children know the test very well because it's part of our clinical routine. But again, I want to stress that the training is very specific on giving strict instructions according to what is specified in the manual.

DR. GREEN: Thank you.

DR. ALEXANDER: Thank you. Dr. Nuckolls?

DR. NUCKOLLS: Yes, I have a question for Dr. Mendell regarding --
DR. ALEXANDER: Could you please just state
your name on the record again?

DR. NUCKOLLS: I'm Glen Nuckolls. So a
question for Dr. Mendell regarding genotypes that
modify disease progression, such as osteopontin and
LTBP4. So you were an author on a publication in
2013 that demonstrated that the major protective
haplotype of LBTP4 is associated with prolonged
ambulation, up to 2 years, a level comparable to
the effects of corticosteroid treatment.

So what is known about the modified
genotypes of the treated and control groups and how
might that information aid in interpreting the
data?

MS. RUFF: One thing I'd like to point out
is the prevalence of these modifiers are very, very
low. But anyway, I will ask Dr. Mendell.

DR. MENDELL: Well, Glen, thanks for the
question. I think what you have to appreciate is
that back in 2010 when we designed this study,
there were no modifiers, and so it was not part of
the original protocol. And then, as the study
evolved and we saw the results, and then compared it to the Italian group and the Leuven group, we had comparable number of patients, comparable age, and as Ed Kaye showed, they were matched demographically in every way.

We appreciate that the modifiers would be equally distributed between the groups. There's 12 in our group, 13 in the comparable control group. And we felt that there would be the same statistical possibility for the modifying mutation to appear in both groups.

So it has not been done, but it could easily be done at any point in time. It's unlikely to have an effect given that the groups are the same size. And in the Italian group, there is no difference in terms of the 6-minute walk and so forth, as you saw.

DR. ALEXANDER: So this is Caleb Alexander. Just to clarify, you don't have information, it's never been studied, for either the control or treated patients, the presence of this genetic phenotype?
DR. MENDELL: At this point, yes.

DR. ALEXANDER: Thank you. Dr. Ovbiagele?

DR. OVBIAGELE: Bruce Ovbiagele. My questions pertain to the nature and the timing of dystrophin, and so perhaps this question might be for Dr. Kaye.

First, I recognize of course that it's the increase from baseline that's the most meaningful determination of treatment effect. But from the literature, do we know what the magnitude of increase from baseline that's most meaningful? That's the first thing.

Secondly, have exon 51 patients actually been studied with regard to that, and what exactly is the clinical relevance?

The last question pertaining to that is about dose and duration. Are there any other supportive data at 24 weeks showing that there's an increase in dystrophin at that time point?

MS. RUFF: So I'd just like to clarify your question. So I believe you had three questions. One was about increase from baseline, are there any
details in the literature.

DR. OVBIA GELE: Right. So on one particular slide, it was pointed out that the increase from baseline is the most meaningful determination of treatment effect, and certain references were cited. So I was trying to figure out what the magnitude of that increase actually is and whether exon 51 patients were actually studied, and what was the actual clinical impact.

MS. RUFF: Okay. So I'll ask Dr. Kaye to come first to discuss the magnitude of effect from baseline, and then Dr. Muntoni to discuss the clinical relevance.

DR. KAYE: One of the challenges of course that we had with this study is there is no information before this therapy was initiated. The reason being is that no other drug has produced dystrophin as a comparator, so we don't have a good comparator to know how much is enough. The only way we can compare is to know what's available in the exon 51 boys and other boys who have certain amounts of dystrophin.
What we do appreciate from the field is that if you have a small amount of dystrophin, what's been recorded in the exon 44 population, that does seem to make a difference. You can prolong ambulation by at least 2 years. So we have to make that comparison by stretching to the literature, but there is no baseline that has been established because no one's really been able to make dystrophin before to compare.

DR. MUNTONI: My name is Francesco Muntoni. I'm a pediatric neurologist. I work at UCL in London. I was a principle investigator the first two clinical trials where this drug was given for the first time to boys with Duchenne. I have received compensation from Sarepta for being here at this meeting, and I have no financial interest in the outcome of the meeting today.

I will address two points from your question. The first is, what is the significance of this increase in this treated boy, and the second is, has other patients with exon 51 been studied.
So regarding the first point, as a person who looks at the biopsy of these children as well, one thing that is unusual in the biopsy of these children that convinced me that there is a functional significance of this level of dystrophin is that not only there is dystrophin at the sarcolemma but there is restoration of protein of the dystrophin associated complex.

So dystrophin is a member of a protein complex, and its deficiency leads to a destabilization of a number of protein associated with the sarcolemma. And in the fibers that have dystrophin, you can see and also quantify using the immunocytochemistry if the protein of the complex have been restored.

I will ask in a second a slide to come up where you will see that there will be black when there is no dystrophin, there will be white at the sarcolemma where there is dystrophin. And you will see that whenever there is dystrophin, the protein of dystrophin, as a safety complex had been restored.
If I can have this slide up, please. So if you concentrate on the left side of the screen, you will see that every single circle on the top with white is dystrophin. The same fibers in the intermediate and lower panel also have other dystrophin associated protein that are not present in the fibers that do not have dystrophin. So that I think is a very powerful argument that that dystrophin is doing something functional.

In terms of the second part of your question, if I understood it correctly -- will you please correct me if I didn't -- so we did look at a patient who have exon 51. They are the equivalent of what we want to do by skipping exon 51. They are Beckers who have the equivalent deletions. And I co-authored the paper that was also cited in the briefing document for FDA.

So when we look in these patients, what we found were two things that are important. The first is that the level of dystrophin in this group of patients was very high in general. The lowest patient was in the range of 40 percent.
However, one important point to make, the great majority of these patients were either symptomatic or had minimal symptoms, and therefore what we concluded is that if you were able to put 40 percent dystrophin, this patient potential could be asymptomatic. So that of course is an extrapolation regarding the treatment now.

Does that answer your question?

DR. OVBIAGELE: No, that's very helpful. And just a last question, please, about the timing of the increase in dystrophin, which was at 24 weeks, which was somewhat contradictory to one of your earlier studies. And I wondered if there any literature supporting that increase at 24 weeks.

MS. RUFF: Dr. Kaye?

DR. KAYE: So again, one of the limitations is that there hasn't been any other drug that has been able to really measure dystrophin. We know that dystrophin lasts a very long time and has about a 2-month turnover, so we know in order for the protein to turn over and to make new one, it's
going to take a fairly long period of time.

What Dr. Muntoni had shown in his laboratory, within the first 12 weeks, you could see some dystrophin. He had a very sensitive assay, but it wasn't as, let's say, reproducible and validated as the second assay that we performed.

But what we saw at 24 weeks is a consistent increase in all of the patients, and this is probably consistent with the half-life. So this was really the first time that this has been appreciated, and, again, because eteplirsen was really the first drug to show dystrophin.

DR. ALEXANDER: Does that answer your question? Okay.

So we'll take a question from Dr. Kesselheim, and then after that, we'll convene for a break.

DR. KESSELHEIM: I just wanted to follow up on the dose question just to clarify how it was that you determined the 30 and 50 milligram dose on the basis of the prior studies that didn't test
that, and then how you determined to choose the
30-milligram dose as the one that you are
approaching. And then my other question is whether
you had a physiologic basis for the 24-week
hypothesis, but I think you addressed that in the
previous discussion.

MS. RUFF: Okay, so Dr. Kaye.

DR. KAYE: So as you can imagine in rare
diseases, dose ranging can be challenging because
you don't have large numbers of patients. So we
had determined early to do a dose ranging based on
the percent dystrophin positive fibers. And what
I'd like to show you is at our week 48 biopsy, we
had a comparison of the percent dystrophin positive
fibers and also the dystrophin intensity.

Slide up, please. In looking at this slide,
in the purple, we see the 30 milligrams and the
50 milligrams. And we see that they were very
similar for percent dystrophin positive fibers and
for intensity.

But obviously this is not a perfect dose
finding, and what we did do is an additional study
to look at 30 and 50 in addition to clinical.
Slide up, please. And when we compare to the
clinical 6-minute walk test distance, if we look at
the 30 and 50, they're very similar.

So based on these data, we decided that we
didn't know if there was any potential long-term
toxicity. We know this would be a lifelong
therapy. We chose the lower dose because we
couldn't see a difference. But I think as we go
forward, we will look at other dose regimens, and
potentially at higher doses, and just to make sure
that we understand how to properly use this drug.

DR. ALEXANDER: Thank you very much. We'll
now take a 15-minute break, so we'll return here at
10:55, promptly. 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 10:55 a.m.

(Whereupon, at 10:40 a.m., a recess was
taken.)

DR. ALEXANDER: We're going to get started.
If everyone can please take their seats, we'll begin with the meeting.

Thank you. We'll now begin with the FDA presentations, and first, we'll hear from Janet Woodcock, director at the Center for Drug Evaluation Research.

**FDA Remarks – Janet Woodcock**

DR. WOODCOCK: Thank you, Mr. Chairman, and good morning. The purpose of today's meeting is for FDA to get expert advice from the committee on a marketing application for the drug eteplirsen.

And what I'd like to do is provide a framework within which to consider these data based on my 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval.

The clinical development program for this product has features that render the data particularly difficult to interpret. It consists primarily of long-term observation of a group of 12 treated individuals.

When a large treatment effect is observed,
for example significant improvement in a disease characterized by overall progression, an uncontrolled study can provide compelling data. Where overall effects are smaller, and especially if there's large inter-individual heterogeneity in the disease course, interpretation of data like this can be challenging.

The sponsor and FDA have attempted interpretation by comparing the results in treated children to the disease trajectory that is recorded in a number of external cohorts. It's possible to reach different conclusions about these comparisons as is being discussed today.

Eteplirsen is intended to improve outcomes in a targeted subset of DMD patients by enabling muscle cells to produce a truncated version of the protein dystrophin, which is missing or present at very low levels in patients with DMD.

There is agreement that eteplirsen does achieve its primary intended pharmacodynamic effect, that is production of a truncated messenger RNA, and this is based on PCR results from muscle
biopsies.

It was originally hoped that this effect would result in a substantial increase in expression of the truncated dystrophin molecule, perhaps to the average level of individuals with Becker muscular dystrophy. This has not turned out to be the case. The increase in dystrophin so far observed is a fold increase over baseline, well below the average dystrophin content in individuals with Becker muscular dystrophy.

Now, it hasn't been established for any given person with Duchenne muscular dystrophy whether a small fold increase in dystrophin will provide clinical benefit, or whether there's a threshold, for example an absolute percentage of normal, that is required to deliver a benefit. This is unknown, and of course the sponsor has just argued based on observing other mutations that perhaps small levels may be associated with benefit.

It's unlikely an absolute threshold can be established given the fact that within muscular
dystrophy, the phenotype, in other words the disease expression, appears to be influenced by factors beyond dystrophin expression, so there are other factors at work.

Interpretation of dystrophin expression has been complicated by many technical difficulties. The FDA has put a huge effort into trying to render the results interpretable, along with the sponsor.

To me, it is remarkable that the field of exon skipping has advanced far into clinical development generally without well-validated methods of determining pharmacologic success, especially when assessing this biomarker requires muscle biopsies in children with compromised musculature, usually under general anesthesia.

There are a lot of questions that still remain, not just about quantitating the Western blot, but also about specimen handling and intra- and inter-muscle variability and results, especially in later stages of disease. There are also questions, and they've been raised today, about the utility of the information supplied by
immunofluorescence techniques in comparison to Western blot, and these questions are going to be quite important today.

The translational science supporting these development programs is inadequate, and this state of affairs is not atypical in rare and not so rare diseases, and it significantly hinders the tasks of drug developers, as well as the FDA, in assessing the results of these programs.

After the presentations by FDA, the sponsor, and the public, the committee will be asked a series of questions about the robustness of the data support marketing approval, either regular approval or approval under the accelerated pathway.

The determination that a drug's approvable from a clinical standpoint is a two-step process. First, a finding of substantial evidence of effectiveness, usually based on clinical outcomes, must be made, as Dr. Dunn said earlier. In the case of accelerated approval, this finding can be made based on substantial evidence using a so-called unvalidated surrogated endpoint, believed
reasonably likely to predict clinical benefit.

Then, the second step after that is determine whether the likely benefits of a drug outweigh the foreseeable harms. And a final approval decision from a clinical basis is whether the benefits outweigh the foreseeable risks.

The issue of substantial evidence for regular approval, in this case we're talking about today, turns on how compelling you find the comparisons to the external cohort data. I believe the committee has experience with this question, and so I'm not going to into it anymore.

Accelerated approval is a more nuanced issue. In the FDA Safety and Innovation Act of 2012, Congress instantiated and statute our accelerated approval regulations, and in doing so urged FDA to apply accelerated approval more broadly, particularly in rare diseases, while maintaining our standards. FDA has never articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit.
In applications of accelerated approval outside of cancer and HIV, FDA has used various types of data, including natural history data, pharmacologic, pathophysiologic, and clinical data to assist with this determination in a wide variety of settings, most of them rare disease settings. The agency has exercised considerable flexibility in applying these criteria of reasonably likely.

In the case before us today, the linkage between the observed levels of dystrophin expression and potential clinical benefit will be explored. If the committee were to recommend that the clinical data represent substantial evidence, then the question of accelerated approval does not need to be taken up by you.

If the committee does not make this finding, then the clinical data generated in this development program that you've heard about this morning may be used as part of the assessment of whether the surrogate of dystrophin expression at a particular level is reasonably likely to predict clinical benefit. And I'm happy to answer
questions later about that statement if you wish.

Finally, I would note that much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective.

There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally who have little say in how the standards are implemented.

The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you've heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated initially and that in fact sometimes we will collectively get it wrong, otherwise accelerated approval would
really have no different standards than regular approval.

I hope these remarks have been helpful, and I look forward to hearing the deliberations. Thank you.

DR. ALEXANDER: Thank you. Next, we’ll hear from Dr. Robert Temple.

**FDA Presentation – Robert Temple**

DR. TEMPLE: Good morning. I'm going to talk about historically controlled trials, generally as a basis for what you would call full approval. The point Dr. Woodcock made that there are other ways to consider this is important.

So this will be a brief discussion of the history of our use of historically controlled studies and the concerns associated with the design, which will I'm sure be quite familiar to the committee. I want to emphasize, I am not in any way addressing the eteplirsen data in study 201/202; that's going to come in subsequent presentations.

Section 505(d) of the Food, Drug, and
Cosmetic Act defines the standards for drug approval calling for substantial evidence of effectiveness. I don't necessarily have to read all this stuff, but it means evidence consisting of adequate, well-controlled studies that allow you to reach a good conclusion.

Adequate and well-controlled studies were actually first defined in regulations in 1970, a long time ago, and they are now in 21 CFR 314.126 in the current regulations. And from the beginning, they've always included as one kind of adequate and well-controlled study, the historical control, which is interesting because a lot of people would have considered those not quite controlled studies. But it's always been part of it, absolutely part of it.

This is what the regulation says. Sorry to have to read so much. "The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable
patients or populations.

"Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrently controlled populations, historical control designs are usually reserved for special circumstances, and the examples include studies of disease with high and predictable mortality, like certain malignancies, and studies in which the effect of the drug is self-evident, general anesthetics, drug metabolism."

Note, although this isn't specifically discussed, that a baseline control trial where a single arm treatment is compared with what would have been expected in the absence of an intervention is a kind of historical control, although it's not generally mentioned.

ICH E-10 went into a number of different kinds of controls, non-inferiority studies and others, but it also spent some time on the historical control and renamed it as a kind of quote, "external control."
It notes several different kinds. One is a population treated earlier. That's really a historical control. A population treated contemporaneously at another institution. That's not exactly historical but it is external. It could be a group outside the study within the same institution. And it identified specifically the baseline control where the patient's course is compared with the expected course, always a difficult thing. And it again notes the design is most clearly usable when the effect is dramatic and rapid.

ICH E-10 goes at some length into what the difficulties are with these trials, and the major one, of course, is the inability to control bias, which is a major and well-recognized limitation of externally controlled trials and in many cases makes the design unsuitable.

It's worth noting the really two distinct aspects of bias. One is bias before the trial, that is, in who you put into the study, and then the other is bias during and after the trial, sort
of bias in the observations.

Bias before the trial refers to patient selection. Who have you put into the trial? But even that is really two issues. One, since you don't really know, you're not randomizing, the groups can be non-comparable in ways that you don't really understand because you haven't randomized. Randomization doesn't always lead to comparability either, but in something like this it's more of a problem.

The other part of this is selection bias; that is, the control patients could be chosen in a way that means they're sicker. That's non-comparability, but it's got a bias in it. So those are two slightly different aspects of it.

As I said, non-comparability of a random nature can go in either direction. It might not favor the treatment. But the guidance, the E-10 particularly, notes that it is well-documented that untreated historically controlled groups tend to have worse outcomes than an apparently similar chosen control group in a randomized study,
possibly reflecting a selection bias.

There are some examples of this of a classic nature. One of my favorite papers was one by Sacks, Chalmers, Smith and coworkers in 1982 that compared randomized trials and historically controlled trials for the same disease, finding results regularly more favorable for the historically controlled trials.

The following figure was created by Dr. Unger from a table in this paper, and it's clear that the results of randomized trials are regularly less positive than historically controlled trials. In the examples given in the paper, there were 10 out of 50 that were favorable for the randomized trials and 44 out of 56 favorable for the historical controlled trials, and that's what it looks like.

The historically controlled trials are on the left, the randomized are on the right. Effective means red. And you can see that in randomized trials in the cirrhosis, surgical treatment to prevent variceal bleeding, in coronary...
artery surgery, and so on, the historically controlled trials almost always do better.

One particular example was a pooled analysis of shunt surgery for preventing bleeding in cirrhotics, and you can see that the bottom line there, which is the historical control, they do much worse than the randomized treatments. My explanation of this has always been that surgeons don't like to lose, so they put healthier people into their control group when they're in control of the assignment.

So it seems very likely that in general in Chalmers' studies, the historical control untreated patients were sicker than the surgical candidates in the randomized trials. Selection bias in this case, with patients being different at baseline, is the only real source of potential bias here. Mortality is objective. We don't think that could have been done in a biased way. But the baseline differences could have been very important.

So ICH E-10 specifically notes that selection of the control retrospectively with the
results known and in hand poses a particular problem.

There could also be biases during and after the trial, and you'll hear discussions of some of these things. But the lack of blinding and the investigator's knowledge of treatment in patients getting the test treatment can also allow bias to affect endpoints if they have subjectivity in them. And many endpoints, even ones you might think are highly objective, have a subjective element, including whether a person's had a heart attack or not, cause of hospitalization, and most of the other endpoints we typically use. That is why we blind the people who decide those things.

You'll hear later a discussion of the possible subjectivity of ability to ambulate. There will be a debate about that, of course. But importantly, expectation bias and motivation can very markedly affect symptoms and performance, and there are some examples I'll show you where that seems to have been the case.

There can also be other biases, I won't
dwell on this, but the choice of endpoints. You
know, in a controlled trial, you choose the
endpoints beforehand. When you're looking at data
after the fact, you can look around.

So in ICH E-10, the overall tone is
relatively skeptical about the use of external
controls for most situations, as is also our
adequate and well-controlled studies regulation,
but both accept them as credible in particular
situations.

What ICH E-10 urges is selection of a
control group for which there's detailed
information: demographics baseline state,
concomitant medications, and steady course, and
you've already heard from Dr. Kaye arguments that
that is in fact what they did; try to assure
similar treatment other than the test drug and
similar observations in the treatment and control
groups. It's not a bad idea to have multiple
external control groups if you can do it; and it
doesn't come up here, consideration of blinded
endpoint reassessment in the treatment and external
control groups, which can be done sometimes.

ICH E-10 also suggests that the main credible use of external controls is when there's ethical difficulty in doing the randomized trial. They strongly urge early randomization, which certainly we've urged in many other cases.

The concurrently controlled trial can detect extreme effects very rapidly and can detect modest but still valuable effects that would not be credibly demonstrated by an externally controlled trial. And ICH E-10 again notes that external control trials are most likely be persuasive when the effect is large.

Just a couple of more examples that have always interested me. This first one was of interest to me because the person who wrote the letter I refer to there was my first attending at Columbia, a guy named David Gocke, an infectious disease guy.

So he wrote a letter to the New England Journal in 1971 about fulminant hepatitis B treated with serum containing antibody to what I used to
call the Australian antigen. They had 9 consecutive cases of acute fulminant hepatitis B. All were fatal even though they did exchange transfusions, gave steroids, and provided other support. Then they treated eight coma patients with the same treatment plus an anti-Australian antigen, and 5 out of 8 survived.

And his letter to the New England Journal says, you know, we thought maybe we were done, but then we were worried that the treatment -- that there's better care, earlier treatment, so we urged a randomized trial, and they did one, in which he participated.

This was published in 1977 in the Annals of Internal Medicine. There were 53 patients at 30 centers. Survival was as follows. In the placebo group it was 9 of 28, or 32 percent, in the people who got the antigen it was 28 percent. There was no effect at all; pretty sobering and hard to understand given the early results.

More recent example, you've all probably read about this, a widely publicized renal artery
denervation device was studied in three trials. The first one was an open-label single-arm study called SYMPPLICITY HYPERTENSION-1. It found an average 3-year fall in blood pressure of 33/19. Pretty impressive. This was in people who aren't responsive to other stuff.

Then they did a randomized trial, device versus no device, but no sham control, and they found an almost identical effect. Finally, they did a randomized trial with a sham control, SYMPPLICITY 3, and they found at 6 months a change of minus 14 in the denervation population versus 12 millimeters in the sham operation. Nothing. So again, sobering on what seems like a very objective endpoint.

Then Dr. Unger has provided me with help on transmyocardial laser revascularization therapy. That's where you make holes in the heart to allow blood to flow, and this is what you do. You use a laser to make holes in the heart and allow blood to go in.

Initially, at least, it required open heart
surgery to use the laser to create channels through the heart muscle, and no one thought you could do a placebo-controlled -- sham-controlled trial -- if you had to do open-heart surgery, so that was pretty reasonable.

The results were very striking. This was effects on exercise tolerance for angina, a typical test for angina. So I'm showing two studies here. One showed a gradual increase over time for 12 months, almost a doubling of the exercise ability, and the second trial shows almost the same thing. The effects were sustained over a year. It really seemed beyond what anybody could imagine a placebo response was.

Then it became possible to do these things without open-heart surgery through catheters. So they did a double-blind, placebo-controlled trial in almost 300 patients comparing 2 doses as well as no treatment, comparing to a sham procedure. And as you can see, there was just no effect at all. All of this is obviously very sobering.

So having said that, we do rely on
historically controlled trials, just as the regulations contemplate. And the question always is, when are they credible enough and when are they not. There are some obvious cases where it's reasonable.

When I was in training, leukemias were always fatal within 3 months, and then there began to be treatments where there were cures. Well, that never happened. You didn't need a control group to know that that couldn't happen.

The first three treatments for metastatic testicular cancer, at least some of which I signed off on, were cisplatin, ifosfamide, and etoposide. They were all based on success rates in people with metastatic disease, who would not have been alive at one year, much less alive and tumor free. And in the case of cisplatin, it was 90 percent tumor-free survival at one year. You didn't need a control group to know that that worked. So those were very, very easy.

Less easy, but we did it anyway, when I was directing the cardio-renal division a long time
ago, we used to approve drugs for stone disease based on comparing the stone rate in the 6 months before they got the drug with the stone rate in the next 6 months or 3 months -- I don't remember anymore -- and we approved the drugs because the differences were large and persuasive. I don't know if we'd still use that trial design today, but we did then and we were perfectly happy with it.

Then, in many orphan diseases where the course is clear and very well-known, we do use these designs. Alglucosidase alpha for Pompe disease in 2006, the endpoint was 1 year ventilator-free survival in 18 treated patients versus 62 historical controls. I didn't put the response rates here, but 15 out of 18 in the treated group survived and 1 out of the 62 in the historical controls survived that time. Pretty persuasive. It would be hard to argue.

There are others. Lomitapide was approved for LDL cholesterol lowering in patients with familial hypercholesterolemia. Huge change in LDL, obviously not something that could happen
spontaneously. And then a treatment of Cushing's disease markedly lowered urinary free cortisol. Again, that doesn't happen in people with that disease. And then deferiprone was approved in 2011 for treatment of iron overload, and again marked changes showing reduced ferritin in something that almost surely would not have changed. So those can be persuasive.

There have been anti-infective approvals where we didn't think you needed to compare the drug to existing therapy. It wasn't a question of relative effectiveness, but where getting rid of the organism was self-evident evidence that the drug worked. So those are all cases where we found historical controls persuasive.

The ones I've cited are typically cases where there were very well-defined diseases with very predictable outcomes, where you really didn't think that the benefits could have been the results of treatments other than the test drug, and where the course was thought to be very variable.

There are obviously, and you're going to
hear one, cases in which there could be a debate about how predictable the course of the disease is in the absence of treatment, and thus whether historical controlled approaches can be considered and would be well supported as stressed in ICH E-10, and that's what the discussion is about. Thanks.

DR. ALEXANDER: Great. Thank you very much.

Next, Dr. Ronald Farkas and Dr. Ashutosh Rao for the FDA efficacy review.

FDA Presentation – Ashutosh Rao

DR. RAO: Good morning, everyone. Thank you for being here. I'm Dr. Ashutosh Rao. I am a reviewer and researcher in the Office of Biotechnology Products at the FDA. I provided the clinical review team with a consult review of the dystrophin bioassays and the supporting assay validation information, some of which that you've seen before and more will be presented today.

The FDA efficacy review will be presented by both myself and Dr. Ronald Farkas, a clinical team leader in the Division of Neurology Products in
I'm going to start by discussing the assay methods used to gather data about biomarkers in the eteplirsen drug development program. Dr. Farkas will then follow up to discuss the biomarker data in detail and the clinical findings that go with them.

Eteplirsen is proposed to increase the production of exon skipped and truncated dystrophin. The goal of my slides is to describe to the committee and the audience how this important endpoint for a proposed exon skipping therapeutic was tested by the applicant, Sarepta.

I will provide an overview of our understanding of the applicant's methodologies, our understanding of the caveats of each of them, our current thinking on the extent to which they can or cannot analytically provide you with reliable data indicating whether exon skipped dystrophin was produced by eteplirsen, and if so, how much.

We would like you to consider these technical caveats as you consider and discuss the
merits of the clinical findings presented by the
applicant and by FDA.

As stated previously by Dr. Dunn and by
Dr. Woodcock, FDA understands that lack of
dystrophin causes DMD and is very interested in
dystrophin as a biomarker and potential surrogate
for accelerated approval for drugs for DMD. Such
an approval would be based on a conclusion that the
dystrophin produced by a drug is reasonably likely
to predict clinical benefit. Reasonably likely
seemingly must depend on the amount, location, and
function of the dystrophin produced by the drug.

It is important to stress the need for
reliable assays and consistent findings to support
potential accelerated approval based on dystrophin
expression. Hence, the first part of the FDA
presentation will focus on FDA's views on the
methods and the results of dystrophin measurement
for eteplirsen.

Our current knowledge of dystrophin
bioassays based on literature and input from
several experts around the world is that a
scientific understanding of dystrophin requires that the method or methods, a combination of methods perhaps, be capable of answering basic questions about the relative levels of dystrophin mRNA and protein, its location, whether the newly expressed dystrophin is increased beyond the baseline levels of trace or revertant dystrophin, and if it is functional in muscle fibers.

This slide lists the three common methods used to show production of skipped messenger RNA and dystrophin protein, reverse transcriptase PCR for mRNA, and protein measurements using either a Western blot or immunofluorescence-based method.

Each is a variation of a standard methodology that's used in most laboratories, but adapted for this large and very complicated 427 kilo Dalton protein. As a reminder, revertant dystrophin, which arises from rare spontaneous restoration of dystrophin in Duchenne patient samples, is also present in each of the samples that's going to be shown today and was shown previously by the applicant and cannot be
distinguished from non-revertant dystrophin using the currently used methodologies being discussed here.

For each method, I will briefly highlight the type of data submitted by the applicant and summarize our current thinking of whether the approach is analytically capable of providing meaningful results. A typical data set from the applicant's qualitative RT-PCR consisted of a gel, as shown here on the slide, showing the presence or absence of the skipped band representing the expression of an exon 51 skipped dystrophin mRNA, which reflects the fundamental and proposed mechanism of action for this drug, eteplirsen.

As you can see from the example data set here and by the red arrows on the slide, the applicant's method is capable of demonstrating whether or not skipped mRNA was produced.

A positive RT-PCR supports eteplirsen's putative mechanism of action, but keep in mind that the method is not quantitative. It does not measure the number of copies of mRNA or test the
stability of this very large and unstable mRNA. It has the largest exon set of sequence in the genome at 79, so it is a very unstable mRNA.

Moreover, the production of mRNA being one step prior to protein synthesis provides no information on the protein itself, no information on whether even protein was made from that mRNA. Or whether that protein was functional, in other words, whether it was capable of functioning as normal dystrophin would in muscle fibers.

In order to detect dystrophin protein, the applicant used either immunofluorescence or Western blotting methods. The next few slides address immunofluorescence. There are two endpoints used by the applicant to present immunofluorescence data, first by measuring fluorescence signal intensity of microscopy generated images using a computer software. The second is by scoring fibers that are either positive or negative for an anti-dystrophin antibody based fluorescence signal.

The applicant's immunofluorescence method is capable of showing the location of dystrophin
protein based on reactivity with an anti-dystrophin antibody. However, it is not designed to be truly quantitative and compared to Western blotting has serious shortcomings when it comes to quantifying the levels of protein. Specifically, the intensity measured by microscopy does not use healthy samples of serial dilution or a reference standard of say recombinant dystrophin protein or a fragment of the protein that one would need to reliably compare and objectively quantify the immunofluorescence signal.

During our review, we noted that the intensity measurements tend to overestimate the dystrophin fluorescence, especially at low levels that are present in untreated and in some treated samples. For instance, immunofluorescence signal may indicate 10 percent of signal compared to a healthy tissue specimen, but it would be far less when the same sample, the exact same sample would be tested by Western blotting.

The second immunofluorescence method used by the applicant reports a score of dystrophin positive fibers or percent positive dystrophin
fibers. This is also a standard technique. It's a standard technique adapted but primarily well-suited to confirm the location of proteins in tissue sections.

On the right-hand side on top here is a processed image of muscle section stained to identify dystrophin. In this case the colors on this image were inverted and amplified by the applicant to allow a pathologist to score the fibers.

You can see that the staining for dystrophin by the applicant localizes to the sarcolemma as would be expected. Staining fibers such as the ones in this image are used to then score them as dystrophin positive or negative. However, the scoring is based on staining intensity and is not an all or nothing type of scoring, and hence the reading is subjective. For instance, fibers can be classified as positive if the staining is only barely above the background, as is the case in some of the fibers here.

The staining between patients, and even
within the same patient but different muscle groups or a biopsy taken on different days, is not uniform and contain a mix of staining intensities. Also, it is simply not possible to differentiate fibers with new drug-induced dystrophin from the spontaneously occurring revertant fiber dystrophin using this method.

In general, for any fluorescence analyses to provide reliable findings, here are some critical factors that need to be part of a predefined study design. The investigators need to be blinded to patient identity and treatment assignment. There should be a systematic and random selection of fields, even better if this is automated.

Control sections with positive, intermediate, and negative samples can estimate the range of the signal obtained by one's test sample. So even though the method is not quantitative, if you were to use appropriate controls, you could at least determine a range of your signal.

Careful consideration needs to be given to how the image is processed, displayed, and even the
consistency and ambient light can be an important factor. Independent reassessment by more than one pathologist and blinded sequence for reading can also help control for inter- and intra-observer variability.

We believe that the data generated from studies 28 and the early biopsies from study 201/202 were largely exploratory, not validated, and not consistent with all these principles highlighted here.

Appreciating the potential significance of dystrophin measurement towards the development of much needed therapies for DMD, we worked very closely with this and other applicants to clarify and improve the scientific credibility of their dystrophin findings.

Following discussions with the applicant and the investigators, we scheduled and visited the laboratory testing site at Nationwide Children's Hospital to assess methodology and raw data where a number of issues were identified. Extensive technical advice was provided to the investigators
during and following the visit.

As has been mentioned before, we also held a NIH/FDA joint workshop bringing together experts in the field to discuss the current state of dystrophin methodologies. Also, with input from external stakeholders, FDA released a draft guidance for industry on developing therapies for DMD that included some guidance on the potential for dystrophin to validate the findings of other endpoints.

Following several rounds of discussion with the FDA, the applicant developed and implemented a technically satisfactory set of methods for immunofluorescence. Specifically, they implemented a systematic and random field acquisition protocol for image acquisition, improved blinding processes, implemented quality assurance steps, and independent reassessment by three pathologists outside the primary testing lab was carried out. The experimental analyses included positive, negative, and intermediate control samples in the form of healthy Duchenne and Becker tissue.
This slide shows an example of data from the applicant's fourth biopsy showing two images on top that are stained for dystrophin and the two corresponding inverted and amplified images on the bottom that were used for the pathologist to identify total fibers.

The images that are on top are stained red where the antibody had reacted with an anti-dystrophin antibody. Both images contain fibers scored positive by the applicant. However, as I stated earlier, it is not possible to differentiate between dystrophin spontaneously present in revertant fibers and drug-induced or newly expressed and truncated dystrophin. For instance, it may be tempting to believe that particular fibers in both of these images represent drug-induced dystrophin, but there is no way to know whether they are revertant or not using this particular method. Analytically, immunofluorescence is unable to tell us whether dystrophin is new or not.
Also, the method cannot provide data on the absolute levels of new truncated protein that correspond to a given fluorescence intensity. From the applicant's data, we can however tell that the dystrophin as present in these samples is localized to the sarcolemma region of the cell or the fiber, which is where you would expect it to be if it were functional.

Overall, we believe that the applicant's overall immunofluorescence methodologies, both of them, are capable of confirming location and are supportive but tend to overestimate the signal compared to other methods and cannot differentiate between drug induced and truncated dystrophin from the other forms of spontaneously occurring dystrophin.

The next few slides cover the Western blotting. The applicant's Western blot measures the relative amounts of this 425 kilo Dalton protein that reacts with an anti-dystrophin antibody. This is the most quantitative method used by the applicant and the best to compare the
relative levels of signal in samples in Duchenne
either before and after treatment, and comparing it
to Becker dystrophy or healthy control samples.

Although this method is technically
challenging, the image shown on this slide from a
1989, as has been said before, is representative of
a significant body of literature that suggests that
Western blotting can be performed reliably using
human tissue.

During discussions with the applicant and
the collaborating investigators about study 28 and
data from study 201/202, several
concerns were identified in the methods that
obscured interpretation of the dystrophin data.

The full length gel image shown on the
right-hand side is an example of Western blotting
data from the bicep muscle tissue of the early
three biopsies in 201/202. On the left is from
study 28. As you can appreciate, the gels were
overloaded and the bands consequently were
oversaturated.

Because this method critically depends on
the presence of clear, distinct bands used for quantitation based on the density of those individual bands, these blots cannot provide reliable quantitation of dystrophin protein. Overall, the methods of dystrophin protein quantitation from the first three biopsies in study 201/202 were not considered reliable, and the results were not considered interpretable.

Here the left image again shows the results obtained before technical advice provided by the FDA. The right side is from a fourth biopsy sample after discussions with the FDA and using deltoid muscle. While this slide should really require no explanation, you can see how the Western blot images from the early biopsies were clearly not discernable to allow meaningful quantitation.

The red arrow on the gel on the right-hand side shows the proposed location of the 427 kilo Dalton protein that was then used for quantitation. We consider the quality of the fourth biopsy set of data to be satisfactory to quantify relative protein levels.
This slide is meant to illustrate why we consider the fourth biopsy data to be reliable, essentially because of the inclusion of a standard curve of serially diluted healthy samples on each gel that are shown on the legend on the top of that gel.

The presence of these serially diluted samples allows the generation of a standard curve. The curve is shown on the right, and the samples were quantitated in the validated range of 0.25 to 4 percent of healthy dystrophin. We also consider the fourth biopsy method to be more reliable because of the inclusion of either a Duchenne or a Becker, and a healthy control in the same experiment corresponding to negative, intermediate, or positive controls to allow a credible side-by-side comparison of relative differences.

The fourth biopsy was acceptable but problems with controls make the change in dystrophin challenging to interpret. Ideally, the change in dystrophin would have been assessed by comparing pre-treatment samples to post-treatment
samples from the same patient and the same muscle, but this is not how the analysis was conducted.

Here are some specific issues that were identified with the choice of controls prior to the fourth biopsy experiments that you should consider. These are important to consider because the applicant is proposing changes in dystrophin levels following eteplirsen treatment when the samples were tested and compared to this set of control samples and not to each patient's matched baseline.

As mentioned before, different muscle groups from treated samples were used for the analysis, including the fourth biopsy where deltoid samples were used in contrast to biceps from the first three biopsies.

As a reminder, there were no deltoid baseline samples for the same patients for comparison and matched baseline samples were used for only 2 of the 11 patients, and those two were from a different muscle group, biceps in those cases.

The DMD negative control samples that were
used for comparison were also from different muscles, essentially including biceps, quadriceps, and deltoid. And the data from all of these different muscle groups were combined for a comparison to the fourth biopsy data that was from deltoid muscle.

The controls were not sex matched because one female sample was included in the set of samples used to calculate the mean healthy value. And even within the healthy control data set, there is variability as was seen in the reported range of 51 to 95 percent.

In summary, at this time, we believe that the applicant's fourth biopsy data methods for the 201/202 study were the most quantitative and were reasonably adequate for determining the relative dystrophin levels for the purpose of their drug development program, with the caveat that there are some issues with the control sample that make it difficult to accurately calculate the change from baseline that could be caused by eteplirsen treatment.
We also believe that immunofluorescence can provide supporting information. It cannot reliably quantitate dystrophin protein levels. It is capable of informing on the location of potentially newly expressed protein.

Overall, a combination of the applicant's methods, immunofluorescence and Western blotting, was considered reasonably capable of demonstrating an increase in dystrophin by eteplirsen.

I will now turn it over to Dr. Farkas to present the clinical findings from the applicant's studies and their relevance.

**FDA Presentation – Ronald Farkas**

**DR. FARKAS:** Good morning. I'm Ron Farkas, a clinical team leader in the Division of Neurology Products at FDA. And the first thing I'd like to say is that I've had the opportunity to talk to Duchenne patients and caregivers at meetings before, and I'm really glad that I've been invited to talk at a parent project muscular dystrophy meeting. And one of the things that I raised at that meeting is it's really important to take a
close look at what you're being told and the kind of analyses that are being done.

That was about a year ago, and there really wasn't really an opportunity to go into the data, and I would have really liked to then. But now we have an opportunity to go closely into the data and the way the data is being analyzed.

I'd just like to perhaps take a slightly unusual approach and go for some slides in the middle of my presentation because I think that what might be in people's mind is that there's a very large clinical effect, that all the control boys are no longer walking and almost all the treated boys are still walking.

So there's going to be a lot of talking, and I'm going to explain a lot of sources of difference between patients in drug trials and natural history trials. So as I go through all that detail, I just wanted to, again, kind of show people right now where I'm headed to and to get people to think about what the observations are showing.

If I could just have slide 67 pulled up.
It's going to take me a while to get to through slide, but I think that one of the key things I'm going to try to explain is that the way to look at this data is to take a look at age of loss of ambulation and not time to loss of ambulation.

One of the things I'm going to be driving at is that contrary to what is suggested by some of the applicant's analyses, there does not appear to be evidence of a difference in age or future age. And that future age is important, future age of loss of ambulation in the eteplirsen patients and controls.

So this graph shows, going from left to right, it shows 6-minute walk test on the Y-axis and age on the X-axis. And it shows going from left to right, basically an alteration between the course of the blue control patients and the red eteplirsen patients.

So kind of going over at 200 meters -- so going over, there's a blue patient and then a red, a red, a blue, a blue, a red, a red, a blue over at 200. And I think one of the -- so let me just step
over here for a second.

So what's going on is that we're comparing two different kinds of Kaplan-Meier curves to each other. I'll explain that in a second, too. But the blue patients have all gone down to zero in 6-minute walk test, and so the red patients haven't, but we have to be very careful about if we're thinking of what their age is or what their walking ability is. Anyway, I'll get back to that in just a minute.

I think the other slide I'd like to show is slide 75. I think the issue here, and I'm going to come back to this later, is the age or the percentage of the patients that maintain ambulation to 16 years old. So what we need to do is try to picture what percentage of the eteplirsen treated patients are going to be walking at age 16. And actually it's older than age 16, so there's been discussion about what age exon 51 patients walk to.

The best numbers that we have are 25 percent at age 16, but actually there's -- and I'll get to these slides later when I go through in order -- is
that 15 percent of patients are walking until age 18.

So I'm going to start going back now to all the details of -- well, perhaps all the small things and all the medium sized things that add up to problems with interpretation. But I think just to start out with perhaps trying to show the way that we've seen the data, that there is not this very large difference in the age of loss of ambulation between the treated patients and the natural history patients.

So I'll go back. Could I have slide 21? Just to go back to the beginning. I'm not going to spend a lot of time describing the studies that were conducted by the applicant because they did that, but I'd like to focus on the advice that FDA gave to the applicant and on the study results.

Phase 1 and 2 studies are important in drug development. Study 28 was designed to identify a route of administration and dose of eteplirsen that might be effective. For most new drugs, and especially those for serious diseases, the dose
should be increased until limited by safety or
tolerability or until there's no further increase
of a biomarker such as dystrophin in this case.
The eteplirsen doses in study 28 ranged from 0.5 to
20 milligram per kilogram per week, with 4 or fewer
patients in each dose cohort.

The study 28 investigators reported
dystrophin levels from zero to 5 percent of normal
in untreated patients, and that's an amount that
fit expectations for the trace levels of dystrophin
that are present in untreated DMD patients. The
investigators also reported finding dystrophin
levels after 12 weeks of eteplirsen treatment of 10
to 20 percent of normal, and that's an important
number to keep in mind because the experts, when
they saw that 10 to 20 percent, they were
encouraged, and that fit the expectations of
experts about the amount of dystrophin that might
result in clinical benefit.

No safety issues were identified that would
limit higher dosing. The highest dose was
20 milligram per kilogram per week. This lack of
toxicity is of course good, but only good in some ways because it also represents a shortcoming, a missed opportunity to study higher doses.

The next study, 201/202, tested doses only modestly higher than 20 milligram per kilogram per week. That is not much higher than in study 28. There were 4 patients at 30 milligram per kilogram per week, 4 patients at 50 milligram per kilogram per week, and 4 patients on placebo.

With only 4 patients per arm, there were too few to learn much about dose response, and that was a question that came up earlier. And in truth, really there's too few to learn anything about dose response. Dystrophin was measured at week 12, as in study 28, and also at weeks 24 and 48. As mentioned by Dr. Rao, these three time points are referred to as the first three biopsies.

The study 201/202 investigators reported that dystrophin increased at week 24 but not at week 12. This was different than study 28, which has been mentioned before, in which robust dystrophin expression was reported at week 12.
Consistency of findings is something that we're going to talk a lot about in these first few slides, and that's a great concern in all areas of science, including drug development.

I think the issue is that without consistency of findings, it's really hard to know if something's true, if just the basic numbers that we're looking at are true. So one of the things that drives the FDA standards is trying to find something that's true, a number that's true, an estimate of dystrophin expression that's true. And the results need to be consistent to know if that's really a true number that you're looking at.

In study 201/202, by week 48, dystrophin levels of 25 to 50 percent or higher were reported in all patients. These published findings seemed highly encouraging, and helped lead the DMD community to the conclusion that eteplirsen was effective and to an understandable reluctance to participate in future placebo-controlled studies. This essentially marked the end of phase 1 and 2 studies for eteplirsen.
FDA learned more about the data in discussions with the applicant about NDA filing and became concerned about the reliability and consistency of the data, communicating this clearly to the applicant. FDA nevertheless agreed to file the NDA based on assertions by the applicant and many DMD experts, of both high levels of dystrophin expression and clear clinical stabilization in the 12 eteplirsen treated patients.

FDA worked with the applicant on more reliable dystrophin assays as described by Dr. Rao. The applicant obtained a fourth muscle biopsy at week 180 of eteplirsen treatment from 11 of the 12 original patients, and as the NDA was being submitted, studied these biopsies with the more reliable dystrophin assays.

In the meantime, detailed review of the study 28 and first three biopsy of study 201/202 findings confirmed FDA's concern that the earlier dystrophin assays were not reliable. For example, as described by Dr. Rao, Western blot bands were oversaturated. Also, regarding dystrophin positive
fibers, immunofluorescence images were captured and read in a way that might have been overly subjective with preferential selection of brighter staining muscle regions.

Now, I'd like to shift though to the way that these dystrophin staining images were captured. Because dystrophin staining fades, only one set of images could be captured from the stained tissue. So there was an independent blinded rereading of the images that were taken, but the issue is how the original images were taken.

So the independent blinded rereading can get rid of bias from the reading, but it can't get rid of bias in the way that the images were originally selected. And that's one of the things that we're concerned about because the original images were not selected in a way that was more or less fully automated that would allow for unbiased selection of images.

One other point that came up was, Dr. Rao had said, that it's not possible to tell the
difference between revertant fibers and
drug-induced dystrophin. And one of the issues
that came up in the question and answer with the
sponsor was talking about dystrophin associated
proteins. And it's true that if there's dystrophin
associated proteins in those fibers, that provides
reassurance that the dystrophin is functional. But
the issue is that if there's preferential selection
of revertant fibers, you'll also see the dystrophin
associated proteins.

So that can tell you something about the
exon skipped dystrophin working, but if you select,
preferentially select the revertant fibers, it
can't tell you if the drug is doing that or if
that's what was present at baseline.

So this is the fourth biopsy results, and
it's one of the most important slides that we're
going to be looking at today. Instead of the
expected 25 to 50 percent normal dystrophin, as was
mentioned before, there was only 0.93 plus or minus
0.84 percent of normal dystrophin in the treated
patients. This was measured by Western blot, the
most accurate method of quantification used by the applicant.

It seems concerning that the fourth biopsy result was so inconsistent with earlier results, and this appears to raise additional important questions and to highlight the need for independent confirmation of findings. The fourth biopsy result was based on one group of patients at one investigative site. No matter how many times a single set of data is reanalyzed, including by independent readers, it does not constitute independent confirmation of findings. It's still just one experiment.

One of the critical questions today is whether eteplirsen produced dystrophin. A dystrophin level of about 0.1 percent was reported in the controls for the fourth biopsy. It's important to highlight, however, that because of the lower limit of reliable detection of the assay was 0.25 percent, it would be more accurate to view the level in these controls as something like less than 0.25 percent.
The reason that I'm spending some time on this is that if one were to compute ratios about how much dystrophin increased, you'd really want to think about the lower level of detection of the assay. So the levels in the control patients was not accurately determined to be 0.08 percent. All that we really know is that it's something -- if it was zero, it might be anything between slightly less than 0.25 percent and whatever number was measured. We just don't know that information because of the assay.

The dystrophin level in the controls was still, even given what I said, lower than the 1 percent in the eteplirsen treated patients. But as discussed by Dr. Rao, the controls were not matched. The tissue came from different patients and different muscle groups such that there is concern that the comparison may be apples to oranges.

It was mentioned before that there isn't evidence that dystrophin levels are different in the different muscle groups that were used, but I'm
not quite sure if that's the right question to ask.
When the applicant first identified using controls
from a different muscle group, we raised concern
about that. And normally when controls are used,
you try to match the controls.

So we advised the sponsor at that time that
unless there was a substantial change in
dystrophin, it would be confounded by using this
different muscle group. And as it happens,
different muscles do progress differently in
muscular dystrophy, so some muscles degenerate more
quickly and some more slowly. And the relative
amount of dystrophin in different muscle groups is
not well-characterized. So there's certainly
reason to be concerned that this was not an
appropriate control to pick.

But I think the thing that we need to focus
on, too, is how little the difference is between
the controls and the eteplirsen treated patients.
So we're talking about something in absolute terms
of less than a 1 percent difference, and that might
get lost when talking about the ratios.
How different were the controls in the treated patients? Well, we know it's less than 1 percent in absolute terms, so that leaves, I think, some question about how similar those controls were.

So as a result, there appears to be uncertainty about how much or perhaps even if any of the 0.93 percent dystrophin in treated patients at week 180 might have been from an effect of eteplirsen versus how much might have been present at baseline.

Again, it should be stressed that we don't have Western blot data from 9 of these 11 patients prior to treatment, so it's really not possible to assess the change in dystrophin in these patients.

Now, let's shift to discussion of percent dystrophin positive fibers, as determined by immunofluorescence. This was the other principle way that dystrophin was assessed by the applicant.

First, as discussed by Dr. Rao, percent positive fibers is not a helpful measure of the amount of dystrophin because a positive fiber does
not mean a normal amount of dystrophin, a
functional amount, or really any specific amount of
dystrophin. It only means an intensity judged by
eye to be above background of the image.

One of the numbers that came up before, too,
was greater than 30 percent of staining, but that's
not a measure of intensity. It's not greater than
30 percent of normal intensity. That's greater
than one-third of the circle of the muscle fiber
having some detectable amount of dystrophin. So
that's something that's just an intensity judged by
the eye to be above background of the image, but
only in a fraction of the muscle fiber. So
two-thirds of the muscle fiber might have no
detectable dystrophin staining.

In the fourth biopsy, the applicant reported
10 percent positive fibers in the eteplirsen
treated patients and 1 percent in the controls.
These were the same samples used for Western blot,
so similarly it's uncertain how much of this
difference might have been from an effect of the
drug versus other differences between the samples.
As you'll see, it also remains difficult to find consistency in the percent positive fiber counts, even with the improved method with three blinded readers.

Here are the results showing percent positive fibers from the muscle biopsies. The results on the left were analyzed by a single reader at Nationwide Children's Hospital. They were read at baseline, week 12, week 24, and week 48. On the right are the rereads from 3 blinded readers shown in blue, at the same time points, week 12, 24 and 48, and then there's also a reading at week 180 of eteplirsen treatment.

In the first three biopsies, the results from the 3 blinded readers found far fewer positive fibers than the original reading, shown in the gray rectangle. So for example, 70 percent here, 23 percent here, and on down the line, 58 percent versus 9 percent.

Percent positive fibers, there was discussion about when dystrophin was produced by eteplirsen, and we've been talking about maybe at
week 12, maybe not at week 12. But actually at week 24, there weren't consistent findings either. So percent positive fibers did not consistently increase at week 24, even within study 201/202.

The numbers of patients here are small, but whereas the results in the blue squares for the patients started on 30 milligram per kilogram per week, they do show an increase at 24 weeks of treatment that wasn't seen in patients who were started on placebo and switched to 30 milligram, or who were started on placebo and switched to 50 milligram per kilogram per week.

So these patients were treated initially with placebo for a 24-week period, but then they were treated with eteplirsen for an additional 24 weeks. So if it was going to be a consistent result, you should see the same kind of increase in the second 24-week period that you saw in this first 24-week period, but the dystrophin positive fibers in fact for these other two groups of patients don't increase at 24 weeks.

The fourth biopsy controls that were
selected by the applicant had 1 percent dystrophin
positive fibers. This is compared to 10 to
15 percent dystrophin positive fibers in the
original matched controls, as shown by the black
rectangle. So that seems like a big difference,
1 percent versus 15 percent, and this is in two
different sets of controls.

That seems to raise some questions, where
did that inconsistency come from? Was it
differences in the methods, or in the reading, or
one thing that we're worried about is it's a
difference between the controls, between the
original controls from those patients and the later
controls that weren't matched?

So there's the same kind of concern with
comparison of the week 180 samples and the
baseline. So, of course, you'd expect and hope to
see a substantial difference in the percent
positive fibers of the biopsies treated for
180 weeks versus those at baseline. But instead,
in the same baseline samples had levels -- or had
dystrophin positive fibers of roughly 10 to 15
percent, whereas the 180 week samples had
17 percent positive fibers. So that seems like no
difference or very little difference.

So let me just summarize the dystrophin
findings. There was 0.93 percent of normal
dystrophin as measured by Western blot after
long-term treatment with eteplirsen with 17 percent
of muscle fibers with at least some detectable
amount of dystrophin.

Because of poorly matched controls, the
proportion of the dystrophin produced by eteplirsen
as opposed to the dystrophin present at baseline
seems uncertain. Thus, it's not clear how much or
perhaps even whether these values represent an
increase over the dystrophin levels that were
present at baseline.

Consistency of findings is key in drug
development, but there is no independent
confirmation of these findings. The week 180
findings appear to be strikingly inconsistent with
earlier reports.

Ratios of dystrophin levels in treated
compared to control tissue that have been presented
by the applicant may be apples to oranges
comparison because of poorly matched controls. The
ratios also lack reliability because of small and
questionably calculate denominators.

As Dr. Rao explained, FDA is very interested
in drugs that might restore dystrophin, and
dystrophin could serve as a surrogate endpoint for
accelerated approval. I think as pointed out by
many speakers today, there's a lot of interest in
the relationship between dystrophin levels and
clinical course, and there are many publications in
this area, but it's important to understand that
when discussing very low levels of dystrophin,
literature reports are not always accurate.

The reports might state that a patient
expressed no dystrophin or only trace dystrophin,
but this may only mean that the patient had less
than some often poorly defined lower limit of
detection of the assay. In addition, reports may
not be precise in describing low levels of
dystrophin. Trace dystrophin levels are often
detected, but trace is not a defined or useful
measure of amount of dystrophin.

So the FDA has relied heavily on what
experts have written in the past about the
association between dystrophin and a decline in
progression in muscular dystrophy, and that's what
a lot of this information is taken from, what the
experts have said. So with the most reliable
Western blot methods, it appears that dystrophin
levels less than about 3 percent of normal would in
most patients be associated with the typical DMD
phenotype.

You may hear today, and have already heard
today, that DMD is milder at the high versus low
end of this range, and FDA can't stress enough that
we're open to evidence that shows this. But from
our review, and really from what the experts have
said in the past, there appears to be little
reliable evidence that DMD is milder at the high
versus low end of the range between zero and about
3 percent of normal.

There does appear to be some evidence that
levels need to be higher. DMD experts previously suggested the need for perhaps 10 percent or higher levels of dystrophin, with expression in most muscle fibers, to predict a milder than average DMD clinical course.

Let me just switch to one slide, to slide 141. So it was brought up that -- so this data is actually immunofluorescence data, and I hadn't intended to show it at first. What we're really looking for, what really allows comparison of different patients to each other, and especially across different studies, we're looking for Western blot data, and that has an internal standard, a dilution standard. It still might be cross-study comparisons, but it allows some sort of more reliable comparison.

So this data here is taken from Anthony. This is the paper that the applicant cited with exon 44. And I think what's striking here, and I think this is the big question, the big question when we're talking about the correlation between dystrophin levels and the rate of decline in DMD.
And that is the correlation. It's taking a look at which patients are doing well, which patients are doing less well, and how much dystrophin is in each of those 2 groups of patients.

So I'm not really sure how reliable this data is, and it is immunofluorescence data, but one of the things to take a look at is the amount of dystrophin in patients that are doing well. This is patient 3 from that paper. And by immunofluorescence, the dystrophin level was getting close to 50 percent, and then patient 4 and 5.

So patient 3 had a Becker phenotype. Patient 4 and 5 were exon 44 skippable patients, and they lost ambulation at 11 or 12 years old. And then patient 1 and 2 had lower levels of dystrophin and were still able to walk. So at these low levels in patient 1, 2, 4 and 5, there seems to be kind of an opposite relationship between dystrophin levels and walking.

Then, what I really want to point to, though, what I think really merits the attention,
is that there's really a concern that patients who
are doing substantially better, they have higher
dystrophin levels. And that's why it's important
to take a look at the details. That's why just
saying that exon 44 patients do better doesn't
really tell you how much dystrophin is needed for a
less severe phenotype.

I think also when we need to keep in mind
some of the things that were discussed more in the
memo, in the FDA memo, and that is that -- I mean,
certainly we don't want to be too pessimistic about
dystrophin that might lead to clinical benefit, but
we really do need --

(Laughter.)

DR. FARKAS: I appreciate that laughter and
I -- actually I want to interrupt myself to say
that, really, what I'm trying to do is -- what I
feel like I'm trying to do is set the record
straight, and try to explain to people the way that
we see the data and some of the things that we're
not real happy about, the way that the data is
often presented, and some of the things that we're
not really able to say to people.

So I think that there's also a risk in comparing exon 44 patients to exon 51 patients. There is a lengthy literature in Becker muscular dystrophy about how the mutation really matters. And the fact that exon 44 and exon 51 are close in numbers, it doesn't really mean that there can't be a difference in the dystrophin. And some of the biggest differences are in numbers that are close together. So that really doesn't tell you what's going on.

So I wouldn't say that it makes it impossible to use data from exon 44 to understand how much dystrophin is necessary in exon 51 patients, but that needs to be considered.

Could we go back to slide 43? So then going back to the percent dystrophin positive fibers, dystrophin positive fibers, it's been mentioned before, it's very sensitive to the subjective view of the person reading it, and it's also sensitive to the conditions of the assay.

So what we've seen is that in DMD, typical
DMD patients can have dystrophin staining anywhere from zero to 100 percent of their fiber. So it's not a very good method to differentiate patients who are going to have a more severe course from patients who are going to have a less severe course.

But what we've seen with the 17 percent number, 17 percent dystrophin positive fibers in the eteplirsen treated patients, that's more typical of untreated DMD. At least in the range of zero to 100 percent, the 17 percent is more typical of untreated DMD. And what is more typical in patients with a milder course, in patients with Becker muscular dystrophy, they have irregular, it is irregular dystrophin staining, but that irregular dystrophin staining is found in basically 100 percent of fibers.

Then there's this issue of the lowest amount of dystrophin that might be associated with the Becker phenotype, and that's really a problematic question to answer. It's not a very helpful question because the truth is that some patients do
well with zero dystrophin. It's that the
correlation between dystrophin and how patients do
is very real, but it's absolutely not absolute. So
there are rare patients with the milder Becker
muscular dystrophy phenotype that have dystrophin
levels near zero.

These unusual cases highlight that there is
often a lack of clear relationship between
dystrophin levels and severity. Mild disease in
these individuals is likely unrelated to -- not the
result of trace levels of dystrophin. So this is
an active area of research, a very important area
of research, but it's really unrelated to the
proposed mechanism of action for eteplirsen.

These half-brothers just demonstrate this
point. They have the same mutation, but their
disease course is very different. Both
half-brothers are dystrophin negative, except for
revertant fibers. So again, this idea of trying to
find the correlation between revertant fibers and
how well patients do, there's been a lot of
interest in that, but there hasn't really been much
ability to find that kind of correlation.

The younger half-brother become wheelchair bound at age 9. The older half-brother remained walking until age 15, walking well still at age 15. Although these cases are rare, it illustrates the complex relationship between dystrophin, other genes, and clinical course.

Now, I'm going to switch to talking about the clinical data, starting with the 24-week placebo-controlled period of study 201/202. As described earlier, study 201/202 was planned as a 24-week placebo-controlled trial in 12 patients, randomized to either eteplirsen 50 milligram per kilogram per week, eteplirsen 30 milligram per kilogram per week, or placebo. Each group had 4 patients.

The primary endpoint was dystrophin expression, but multiple clinical endpoints were also measured, including 6-minute walk test, the North Star Ambulatory Assessment.

The prespecified clinical endpoints of study 201 at week 24 and study 202 at week 48 were
negative. The applicant performed a post hoc analysis based on a number of major changes, including removing two patients treated with eteplirsen who deteriorated rapidly, and picking a time point to analyze that was outside the control trial period.

FDA explained that these types of changes did not appear reasonable, even for hypothesis generation, and that the post hoc analyses were not interpretable. However, the applicant announced the post hoc results generating considerable public attention.

Now, let's consider the clinical data from long-term open-label treatment with eteplirsen in study 201/202. As others from FDA will also stress today, it's important to make clear that FDA consistently and strongly encouraged the applicant to perform an adequately powered, randomized, double-blind, controlled trial, and expressed strong doubts regarding the interpretability of comparisons of patients in study 201/202 to external controls.
I should add that we gave that advice when we already saw how patients were progressing, so we were open. We are open to data that could be -- we are open to an effect that could be large enough to be interpretable in a historically controlled trial. But what we saw that that didn't seem to be occurring, we gave very strong and very consistent advice to the applicant that we didn't think this was going to lead to an interpretable comparison to historical controls. So again, as I mentioned, FDA is receptive to interpretable data from externally controlled trials.

FDA also explained to the applicant that data from externally controlled trials in DMD may only be interpretable if a relevant objective endpoint, obviously insulated from bias, demonstrated compelling data that were clearly outside the known variability range for DMD. And I'm going to spend quite a lot of time talking about the amount of effect that can be introduced by endpoints that are partially subjective.

So FDA's advice has been entirely consistent
with what is known about externally controlled trials, including in muscular dystrophies. DMD experts, and we have been looking at the advice of DMD experts, have noted that physical function may be affected by simply being in an efficacy study. Patients outside of efficacy studies can perform worse for reasons that are not well understood.

This example is from studies of facioscapulohumeral muscular dystrophy. The investigators wrote, "Whereas natural history data showed a decrease in strength over one year, there was in the efficacy studies an apparent increase in strength in both the placebo and treatment groups."

So this is the kind of difference, the difference of an increase versus a decrease. It's a binary difference, and even that can occur when comparing patients who are in a drug trial to patients who are in a natural history cohort.

The DMD experts went on to say, "Patients in clinical trials in FSHD may have better outcomes than those in natural history studies regardless of treatment assignment, emphasizing the importance of
placebo groups."

The observations of DMD experts also guided FDA advice to the applicant that ambulation was a particularly problematic endpoint in externally controlled trials in DMD. This is a near quote from one of the publications and from talking to experts. This is because near the age at which patients lose ambulation, loss of walking is not a sudden hard endpoint. Preservation of ambulation and other skills is affected by subjective decision making from families and caregivers about those skills, with such factors as risk of falls and injury from continued ambulation weighed against the safety and speed of allowing patients to use a wheelchair.

It was mentioned before that recovery of walking after a fracture might be an indication of efficacy. And we've taken a look at this, but there are other ways to look at that same kind of data. People or patients who experience fractures, that might mark a reasonable time, based on clinical judgment, for that patient not to walk
because they got a fracture.

So there are a lot of decisions that need to be made, too. It's not just a fracture leads to loss of ambulation. It's really a fracture leads to a series of clinical decisions about what to do. And concern about a fracture leads to a series of clinical decisions about what to do.

I see some heads shaking out there. This is the advice that we see, the information that we see in publications, people trying very hard to try to get kids walking again after they have a fracture, and that seems to be something that's possible to do in many cases, not all, if one's mind is set on it.

In a randomized controlled study, the only major difference between the treatment groups is the presence or absence of the drug. In contrast, for an externally controlled trial, there are potentially many differences, both known and unknown, between drug treated patients and controls.

To understand if there's evidence of drug
efficacy in an externally controlled trial, it's absolutely necessary to study the sources and possible sizes of non-drug related differences between groups. A few examples of non-drug related differences between the study arms in study 201/202 follow, and others are described in the FDA memos.

I should just add that looking for these differences, that's just absolutely critical to try to understand if drugs work or not. It's not something that the FDA could avoid doing. It's something that we need to look into.

So first, interpretability of externally controlled trials -- for an interpretable externally controlled trial, it's necessary that efficacy endpoints be assessed the same way in the groups being compared. So that's fairly obvious, the things that are being compared have to be similar to each other. They have to be measured similarly to each other for a fair comparison.

One reason that 6-minute walk test is problematic is that the decision to ask a patient to attempt to perform the test, to attempt to do
6-minute walk test, versus deeming the patient unable, is based partially on judgments and attitudes of the investigator, patients, and caregivers. Moreover, the distance walked could depend on motivation and cooperation.

The FDA's concerned that there may have been important differences in how such decisions were made for eteplirsen treated patients compared to external controls. And this is something that came up in the applicant's discussion earlier. I'd just like to talk a little bit more in detail about it.

So I'm going to focus on two specific patients, but it's important to understand that the issue of endpoints being assessed differently is not limited to these two patients. It's just that there is more evidence of a difference for these two patients.

Two of the 13 control patients selected by the applicant were able to perform 10-meter run/walk reasonably well but were deemed unable to attempt 6-minute walk test. Data for one of these patients is shown in the table.
So at age 10, this patient walked 10 meters in 10 seconds, and walked 356 meters in 6 minutes. But age 11, the patient walked 10 meters in 12 seconds, which is still a reasonable walking ability, but was said to have lost ambulation as measured by 6-minute walk test.

So there's been some discussion earlier about how far patients might be able to walk, or if patients could walk, or I think what the real discussion was is that it wouldn't be unusual to lose ability to do 6-minute walk test before one lost the ability to do 10-meter walk/run. And I think one thing to point out before I get to some more of the numbers, there's not very much difference between walking 10 meters in 10 seconds and walking in 12 seconds.

So there's a 6-minute walk test. If you calculate it out distance that somebody could walk if they were given multiple 12-second intervals, you'd think they should be able to walk something more than none, if given the opportunity to attempt to walk for 6 minutes, that there could be some...
distance recorded.

    This is also talked about a little bit more
in the memo, and I'd like to call up a slide that
was in the memo, slide 125. So this is also from
the Italian cohort, and there are some patients
here who walked 12 seconds, and then 6-minute walk
distance is down at the bottom.

    So there's certainly a range of values here.
One patient who did 10-meter run/walk was walking
about 125 meters on 6-minute walk distance. But
there really is a whole range, so if you trace
12 seconds over, and then down, there's also
patients who did 10-meter run/walk in 12 seconds
who were walking more than 300 meters in 6-minute
walk test.

    So that's one of the reasons that we're very
concerned about when patients are deemed unable to
do a test because when the test isn't measured, you
really don't have any way of knowing what distance
the patient would have walked.

    Of course, too, the way that the applicant
is counting ambulatory versus non-ambulatory, these
Kaplan-Meier curves or other graphs, that's based on the 6-minute walk test. So that's based on deeming the patient unable to walk.

So that gets right back to the whole issue of clinical judgment, that the patients aren't expected to be able to walk, so 6-minute walk test isn't attempted, so there's the conclusion that the patient is no longer ambulatory.

Could I have slide 57? So I'd just like to switch a little bit now to the impact, or possible impact of differences in supportive treatment. So supportive treatment, including steroids, can have important effects on slowing disease decline in DMD.

The issue that FDA would like to point out is that there are some differences in the supportive care received by patients in the eteplirsen trial and patients from external natural history studies. One example is that the eteplirsen patients were treated with steroids for about a year longer, and that could be important for maintaining ambulation.
But that's not really the key point that the FDA is trying to make. The key point is really that small differences, seemingly small differences in care that patients receive can seemingly lead to larger than expected differences in the disease course and in the age of loss of ambulation.

Can I have the next slide? So this slide shows some recent observational data from the Cooperative International Neuromuscular Research Group, also known as CINRG. The investigators compared the course of patients on different steroid regimens to try to determine which might be the most effective. What they concluded is that seemingly small differences in patient care can confound interpretation of observational data in DMD.

This is data taken from a larger table, but it shows two groups of patients who seemingly have a very similar steroid treatment, deflazacort that was given daily, or deflazacort that was sometimes given daily or switched to every other day or some other dosing regimen.
But the point is these patients, they're not exon 51 patients, but groups of DMD patients with seemingly similar care and not selected for any particular mutation, that there was a two-year difference in loss of ambulation between these patients.

So based on this data, and similar data that the DMD experts showed, they concluded that differences in standards of care and dosing complicate interpretation. This study emphasizes the necessity of a randomized, blinded trial of glucocorticoid regimens in DMD.

The eteplirsen data are similar in some ways, including the small sample size. So that there were just 8 patients in this group, that might have led to an unstable estimate of age of loss of ambulation, but there's that same kind of concern in the small eteplirsen study. Thus, even a two-year difference in age of loss of ambulation between eteplirsen treated patients and external controls may not be a drug effect.

There can be other perhaps less obvious
sources of differences between study arms that can confound interpretation of externally controlled studies. Patients who are not motivated, able, or qualified to enroll in drug studies may remain in natural history studies. So one of the things that's important to consider is that drug studies and natural history studies were being conducted at the same time when data for these groups of patients was being collected.

Patients who have progressed more rapidly may be over-represented in natural history studies if they no longer meet eligibility requirements for drug studies. Again I'm going to talk about a specific example, but it's important to stress that this is not limited to these specific patients; rather it's only that there is clearer evidence of differences for some patients than for others.

One of the 13 eteplirsen controls lost ambulation after 1 year and stayed in the observational study for several years, long enough to enable matching to eteplirsen patients. Two other exon 51 patients had similar baseline age and
6-minute walk distance, but discontinued the observational study to participate in drug studies, and were therefore not under observation long enough to potentially be controls for the eteplirsen study.

It even goes beyond matching. They weren't there for long enough to enable matching. You can only do matching to patients that remained in the observational study for the same amount of time that patients were treated with eteplirsen. So the concern is that the only patient out of these three who was available to be matched to the eteplirsen patients was the one who definitely had a rapid decline in ambulation.

Here's an important point. Different analysis approaches are needed for externally controlled trials than for randomized, double-blind, placebo-controlled trials. As just discussed, in externally controlled trials, data may be gathered differently from each group, and groups are different in ways that are impossible to fully understand or measure.
P-values, sensitivity analyses, the kinds of evidence that we're used to looking at from randomized placebo-controlled trials, they can only tell you that there's a difference between the two sets of numbers, but they can't tell you where that difference came from.

So again, the important part of the randomized placebo-controlled trial is it's a really good way to get the two groups of patients the same. You don't know all the differences, but you've sorted one part of the patients to one arm, one part of the patients to the other arm randomly, and that takes care of most of the differences.

Then the p-value can be interpretable. It can tell you something about the chance of seeing the size difference that you might see. But when you start out with patients that are different from each other and where the endpoints have been measured differently from each other, taking a look at the p-values doesn't give you the kind of information that you need.

The key question to ask, really, the only
question that can help in a situation like this -- and we are open to historically controlled trials at FDA. But the question that needs to be asked is kind of what we're going through right now, how big were the differences between the patients at baseline? How many differences were there during the course of the study? You have to use your judgment about how big those differences were. And then take a look at the difference in the endpoints between the two groups of patients and try to decide if it was from some of these known or unknown sources of differences between the patients or if you're convinced that it was from an effect of the drug.

So now let's turn to the figure, some of the figures that I showed earlier, that compare the clinical data from the eteplirsen patients and external controls.

The applicant has shown these 6-minute walk test data as a function of time on study, but showing by age is more meaningful because loss of ambulation is correlated with age in DMD, and so
it's important to adjust for age.

The patients and controls in the study varied widely by age at baseline from as young as 7 to as old as almost 12 years old. In the context of DMD, these are very different ages. So when we're talking about just the original baseline matching that was done for the patients, the patients were matched by quite a range, 7 to 12 years old, so that's not really very close matching for the DMD.

So that's one of the problems with the way the applicant's presenting the data, and what we really need to do to understand the course of the patients is compare patients who are of similar age.

So in these slides, patient's age is shown on the X-axis, and the 6-minute walk test is shown on the Y-axis. The red lines show eteplirsen patients and the blue show the applicant's external controls. Each line begins at the patient's age at enrollment and continues through 4 or 5 years, depending on the available data.
As described earlier, there are many reasons why there may be very real but not drug-related differences between eteplirsen and control patients. Differences in the way the endpoints were assessed are highlighted here. Patients marked with an X -- so this patient's marked with an X, so those were the two patients who were described on slide 56 who had 6-minute walk test values of zero assigned when they could still walk fairly well as measured by 10-meter run/walk.

The patients marked with question marks, these three patients, those were patients in whom 6-minute walk test was assigned zero based on a yes/no question, was this patient walking at year 4?

The problem is that that's comparing data that was measured differently. It's simply not possible to know if the value would have been the same if 6-minute walk test had been measured under the same careful testing procedures used for eteplirsen patients, including, as brought up before, that all eteplirsen patients were tested
twice at most visit.

Because of many types of non-drug related differences, including the way endpoints were assessed, these figures may really be apples to oranges comparisons. So we're going to continue to show the data that we have, but there's a great deal of uncertainty in the similarity of how these data were obtained, if they really represent measurements of the same thing. This is important to keep in mind.

The arrows in this figure are only there to illustrate that some patients declined in 6-minute walk test earlier than average, some about average, and some older than average across a wide range of ages.

Importantly for eteplirsen and control patients, there appears to be a general similarity in age and rate of decline. So again, if we take a look at going all the way across here -- and again, part of the issue of comparing these two groups of patients is that the natural history patients, a lot of those patients were from past history, so we
know the course of those patients. We know the age at which they lost ambulation.

One of the things that we really need to think about when we're making comparisons about the patients who are currently walking and the patients who are not currently walking is that the patients who are not currently walking, they were measured in some cases years ago, and the patients who are still walking are at similar or younger ages, but they're measured now.

So again, taking a look at the course of the different patients, we have the age at which patients are starting to decline and the general course of that decline. And it really more or less alternates with blue and red and blue and red across most of this figure.

I showed this before. So it doesn't look like there's this binary kind of difference in age of loss of ambulation between eteplirsen treated patients and historical controls.

There's no bigger apples to oranges comparison than comparing walking in an 11-year-old
patient with DMD to walking in a 15-year-old with
DMD, but that's what is done with some of the
applicant's analyses. Instead we need to compare
eteplirsen patients to controls of similar age.

So the 11-year-old, marked by the arrow
here, appears to be progressing about the same as
the controls on either side. So there are blue
patients here, and then there's a red eteplirsen
patient, and blue controls here. It's simply not
correct to say that the 11-year-old is necessarily
doing better than these 15-year-olds because it's
confounded by age. The 11-year-old is still 11 and
it's hard to know what's going to happen when the
11-year-old becomes 15.

Then going along the patients, the same
comparison can be made for these two 12-year-old
patients marked by the arrows. They are
progressing at a rate similar to control patients,
and in fact for these patients the lines are
basically overlapping here.

More or less the same comparison can be made
for these 13 and 14-year-old patients. And it's
important to say again it doesn't have to be exact. There's concern that the patients were measured under conditions that were different. But the general course of progression, even in these patients, these 13 and 14-year-old patients marked by the arrows, is similar to the natural history patients.

So now for some patients, the ones in the oval here, there may be differences in reported 6-minute walk test for eteplirsen and control patients. Again, it needs to be remembered that there were differences in the way that these values were assessed.

So the FDA is certainly keen on looking at the data in different ways to see if there's a change in the average age of walking of patients, treated patients, or to see if maybe only some patients are responding in a way that could be clearly attributed to drug.

So it's been suggested that the performance of some eteplirsen patients is very different from the natural history of DMD. So there are one or
two patients, eteplirsen treated patients, who are currently walking at an age when none of the 13 natural history patients selected by the applicant are walking.

But unfortunately, there's recent data that suggests that this is still what can be expected from natural history patients. What we have to do is take a look at other groups of natural history patients, and I think that's the same thing that we're talking about with consistency. It's really necessary when taking or trying to interpret historically controlled trials, to take a look at the variety of different kinds of natural history experience to try to understand the variability between groups.

DR. ALEXANDER: Dr. Farkas, I'd just like to ask you to be mindful of the time as we proceed.

DR. FARKAS: Sure.

Okay, so this is the Kaplan-Meier curve that we saw before. A key point is that the age of loss of ambulation in exon 51 skippable patient appears to be older than is sometimes realized. And that's
really a huge point to be made, and we've heard experts talk here today, but I think the bottom line, and perhaps to save time, is that we've been looking at all the data that we can get about the age of loss of ambulation in exon 51 skippable patients. And from the CINRG data, 25 percent of exon 51 boys are walking at 16 years of age, and 15 percent are walking at 18 years of age.

This I showed before, the kind of interpretation that seems appropriate is to try to figure out what percent of the eteplirsen patients would be walking at 16 years of age.

Other historical data appear to be generally consistent with the CINRG data. The exon 51 skippable patients in the placebo arms of recent randomized placebo-controlled studies of drisapersen that this committee talked about in November, they seemed to also indicate that patients can walk to 16 years of age. And then that group is described more in the memo. They were younger patients who still had well-preserved rise times and 6-minute walk test that seemed
generally consistent with the Kaplan-Meier curve for the CINRG patients.

There's also data being collected about the natural history of muscular dystrophy from the MD STARnet program of the Centers for Disease Control and Prevention. And I'll skip over some of this data, but we can refer to it later if we need to.

But the key thing from this data is that there were 26 exon 51 patients identified, and out of those 26 patients, 3 patients were walking at or beyond 14 years, and 2 of these 3 patients were walking at or beyond 16 years. And also out of these 26 patients, there's still 15 who are still ambulant. So the number of these patients who might ultimately be found to be walking past age 14 or age 16 might be more than that.

So we were talking about correlation between dystrophin levels and change in 6-minute walk test. This is just an exploratory analysis done by the FDA. There's change in 6-minute walk test found versus dystrophin expression, and we didn't see a correlation. And this is a very small data set,
but this is the kind of data that if you saw a correlation, that's the kind of correlation you'd like to see, to understand if there was a difference in the small amounts of dystrophin that we see, that we might see.

So other functional endpoints can be very important. NSAA may be a particularly important measure of disease progression in DMD because it measures the number of underlying abilities related to muscle strength and to safe and practical walking. And in the eteplirsen study, it may be a more reliable measure than 6-minute walk test because it was more consistently measured, with fewer, although some instances of zero being assigned without the measurement being conducted.

So the arrow here indicates what appears to be a generally similar slope of decline for both treated and control patients. You'll notice that more control patients are to the left of the figure, but that's because of lower mean baseline scores in the controls. So that itself is something important to take a look at.
On this slide, we did take a look at the NSAA score by years on treatment, and you can see that there's a baseline imbalance between the two groups of patients, with the control patients a little bit lower on the NSAA score at baseline. And this is one of the kinds of differences that could also lead to the control patients not doing as well over the course of the study.

So this slide is a little bit complicated, but it takes a closer look at, again, the FDA also trying to figure out are there some patients -- patients who are the oldest that are doing the best, are there some patients who might suggest that the course of decline in the treated patients is less than could be expected by natural history.

I think that the main point of this is that there's a similar decline in NSAA score and a fairly dramatic decline in NSAA score even for the patients who were walking relatively well. So the NSAA score in these patients is down at 10 or 9 or so, and that indicates a substantial loss of
walking ability.

So even though at this time, the 6-minute walk test is relatively well preserved versus other patients, there's really no clear indication that these patients would continue walking beyond the known natural history of exon 51 patients.

Ability to rise from the floor may be another useful measure of disease progression in DMD. Lower values indicate a better score and more horizontal course indicates slower progression. So it's notable that two of the patients with the most preserved rise time at older ages were historical controls.

This graph also shows how it looks like there may be a difference in how endpoints were assessed for eteplirsen patients versus external controls. Six of the eteplirsen patients have rise time values of more than 25 seconds, just these patients here, whereas none of the controls have a value larger than 25 seconds, and that's delineated by the dotted line.

We can't know why there was this difference
in the maximum values measured. The protocols and case report forms from the Italian and Belgium studies were very brief and don't provide details about that. But we do know that in a different natural history study, in the CINRG study, 25 seconds is indicated in the protocol as a time beyond which testing of some endpoints might not be considered.

FDA recently received data, additional data from the CINRG study for 10-meter run/walk, rise time, and 4-step climb. FDA is still in the process of analyzing this data but would like to present some initial observations.

Prior to the receipt of the data, the FDA made a prespecified plan for the matching, so that it will be a fair matching not based on FDA looking at the data. And that was based on exon 51 skippable, ambulatory at baseline, baseline age 6 to 12 years, and 10-meter run/walk time less than 10 seconds. 10-meter run/walk was considered the primary comparison because there wasn't much 6-minute walk test data currently available in the
CINRG database.

So here, the 10-meter run/walk time is shown on the Y-axis, and age is shown on the X-axis. Lower values indicate better performance. The red lines show the course of eteplirsen patients, and the blue lines show the course of the CINRG controls. The lines show the results for the 10-meter run/walk test that were actually attempted, not deemed as unable. And the circles at the ends of these lines, those indicate patients in whom the next value was imputed as unable.

The course of 10-meter run/walk appears to be similar for eteplirsen treated and CINRG patients. You can see many CINRG patients tracking with the eteplirsen patients, including the patients who did best was a CINRG patient. But there's a wide range of different courses, but basically overlap of the red and blue lines.

Again, eteplirsen patients were measured the higher values, but this may reflect a difference in when patients who were deemed unable to attempt the endpoint. And there are patients from the CINRG
study that had the best preserved function on
10-meter run/walk.

Now, we're looking at rise time, and the
course of rise time also appears to be similar for
eteplirsen treated and CINRG patients for values
that were measured. The CINRG patients looked much
like the external controls from Italy and Belgium
also that were shown in slides 88 and 89. Note
that none of the CINRG patients are attempting the
test once the rise time reaches 20 to 25 seconds.
And this is the course of 4-step climb, which also
appears to be similar for eteplirsen treated and
CINRG patients for values that were measured.

I'd like to move on to, again, conclusions.
And I know that I've tried to explain things
quickly and I think shown clearly that I think you
haven't heard the whole story, for many years that
you haven't heard the whole story.

But I really do want to reassure everybody
that I remain open to what we hear from the
community, and I remain open from what we hear from
the applicant. And I've made no final decision and
nobody else on the review team has made any final
decisions about what they think about the data.

From the placebo-controlled portion of
study 201/202, including from the applicant's
post hoc analyses, there does not appear to be any
evidence of efficacy for eteplirsen.

Interpretation of the externally controlled portion
of study 201/202 must keep in mind the limitations
of an externally controlled study, which are well
known and detailed in FDA guidance and
international guidelines, such as ICH E-10.

Based on an assessment of all the physical
performance measures, disease progression appeared
to be similar for eteplirsen treated patients and
external controls. All eteplirsen patients who
have maintained ambulation are still well within
the age range in which exon 51 skippable patients
appear commonly to walk.

It does not appear possible to conclude that
differences in physical performance between
eteplirsen treated patients and external controls
resulted from an effect of eteplirsen instead of
from other differences and influences, both known and unknown, between the groups, both at baseline and during conduct of the study.

Regarding general drug development considerations, this is very important. It's really one of the most important slides here because what we have to remember is that we're developing these drugs -- we need to develop these drugs as thoroughly, as effectively, as efficiently as possible. Dose limiting toxicity from eteplirsen was not observed at the doses studied. Higher doses and more frequent dosing could hold promise for the future. Thank you.

So I'd like to introduce Dr. Bastings, the --

DR. ALEXANDER: I think we'll wait actually for that, but thank you very much for your presentation.

DR. FARKAS: Thanks.

DR. ALEXANDER: So I'd like to suggest that we break for lunch, and then when we resume after a 45-minute break, we'll hear from Dr. Bastings, as
well as have an opportunity for clarifying
questions for the FDA.

So we'll return at 12:45. I'm sorry. We'll
return at 1:45. Please take any personal
belongings you may want with you at this time. And
committee members, please remember that there
should be no discussion of the meeting during lunch
amongst yourselves, with the press, or with any
member of the audience. Thank you very much.

(Whereupon, at 12:57 p.m., a lunch recess
was taken.)
AFTERNOON SESSION

(1:48 p.m.)

DR. ALEXANDER: We're going to begin with the afternoon portion of the committee. Thank you very much, and welcome back.

So we'll continue where we left off with concluding remarks from the FDA. I'd like to ask Dr. Eric Bastings to come to the podium.

FDA Presentation – Eric Bastings

DR. BASTINGS: Good afternoon. My name is Dr. Eric Bastings. I am deputy director of the Division of Neurology Products. Duchenne muscular dystrophy is a serious and devastating disease with profound unmet medical need and no approved treatment.

Great hope was raised by early reports by the applicant that with eteplirsen treatment, dystrophin numbers were increased to levels as high as 50 percent of normal and that the course of the disease had stabilized, effects which would have been unprecedented for Duchenne muscular dystrophy.

FDA provided extensive discussions and
guidance during the eteplirsen development program. Just between 2013 and 2015, FDA held 13 formal meetings with the applicant about eteplirsen. As was discussed earlier by Dr. Rao and Dr. Farkas, FDA identified significant methodological concerns about the biomarker assessment and provided extensive guidance on methods for collection of additional biomarker data. Eteplirsen's development program also benefited from extensive involvement and guidance from senior FDA management.

Study 201/202 was also the object of extensive discussions. After study 201 did not meet its primary clinical endpoint, and as FDA did not consider the post hoc analyses conducted by the applicant to be scientifically valid, FDA advised the applicant to conduct an adequately controlled, adequately powered, randomized placebo-controlled trial to assess the clinical benefit of eteplirsen.

At the time, the company heard the view that a placebo-controlled trial would not be feasible, that few, if any patients, would be willing to
participate in a second placebo-controlled trial because they already felt so strongly that eteplirsen was effective. This was an unfortunate situation.

The publication of the results of study 201 may have led to this perception. It stated that after 48 weeks of eteplirsen treatment, 52 percent of muscle fibers seemed positive for dystrophin, and that 6-minute walk distance was augmented by 67 meters.

Unfortunately, as explained by Dr. Rao and Dr. Farkas this morning, there were problems with these conclusions. In any case, the applicant instead elected to continue open-label administration of eteplirsen in study 202, which has now been ongoing for over four years and is proposing approval primarily based on the post hoc comparisons of patients in study 201/202 to an external control.

Many of you may be wondering why the public is only hearing now about such extensive FDA concerns about eteplirsen and why only after the
NDA has been submitted. Because of laws governing trade secret, FDA is generally unable to provide any information to the public about its finding regarding drugs under development and is unable to comment about information provided by the drug developer.

Because of those restrictions, some decisions or positions taken by the FDA, or FDA's silence, might be construed by the public and the patient community as a lack of caring, a lack of understanding, or a lack of expertise when they simply reflect a legal restriction against sharing commercial confidential information with the public.

Advisory committee meetings, such as today, provide a unique opportunity for FDA to discuss with a panel of advisors developer data and FDA views on these data, and we very much look forward to hearing from the committee later this afternoon.

I would now like to briefly review with you the evidence that was provided this morning and discuss why we came to very different conclusions
than those of the applicant. So let's start with the biomarker evidence.

We agree that there is evidence of production of exon 51 skipped mRNA with eteplirsen treatment, supporting its proposed mechanism of action. The method, however, does not show how much RNA was produced or whether this mRNA led to production of dystrophin.

After 3 and a half years of treatment, the proportion of muscle fibers with detectable dystrophin, identified by immunofluorescence, was 17 percent of normal plus or minus 10 percent. As was discussed by Dr. Farkas, it is not clear whether 17 percent constitutes an increase from baseline. Also, as discussed by Dr. Rao, this method is most useful for showing location of dystrophin in the muscle and has major shortcomings for quantifying dystrophin.

Therefore, we believe that the most relevant measure of dystrophin for you to consider is the amount assessed by Western blot. That amount after 3 and a half years of treatment is 0.9 percent of
normal, plus or minus 0.8 percent. That number, which became only known to FDA after the NDA had been submitted, is very disappointing and far lower than estimates presented earlier by the applicant.

The biomarker data are important for the committee to consider. As you've heard, if we believe that the biomarker data are reasonably likely to predict clinical benefit, it would open up the prospect of accelerated approval.

There are two parts to this question. First, is there adequate evidence that eteplirsen produced dystrophin? And second, was the amount produced reasonably likely to predict clinical benefit?

There are some aspects of the data that can be considered that if positive would support the reasonably likely question. If there were a correlation between the amount of dystrophin detected in the muscles of individual boys, and preservation of their physical abilities, such a link would help support the concept that the amount of dystrophin detected was reasonably likely to
predict clinical benefit. So let's briefly discuss an exploratory analysis FDA conducted.

In the figure, which was shown on Dr. Farkas' slide 80, the amount of dystrophin as measured by Western blot is shown on the X-axis, and the change in 6-minute walk distance is shown on the Y-axis. For the 4 patients with the best preserved 6-minute walk distance, at the top of the figure, 2 had among the lowest dystrophin levels, and 2 the highest, as indicated by the arrows.

The data are sparse, but there doesn't seem to be much of a correlation between dystrophin levels and change in 6-minute walk test in this particular group of patients.

You haven't seen this figure before, but as you recall, patients in study 202 received either 30 or 50 milligram per kilogram of eteplirsen for some 3-plus years, so it is worth considering the dose response for the dystrophin detected at week 180. If there were a correlation between the dose of eteplirsen administered and the amount of dystrophin detected, this would help support that
eteplirsen produced the dystrophin that was detected.

Again, the data are sparse, but there is no support for dose response here. Had a dose response been present, it could have helped support a concept the eteplirsen treatment was in fact responsible for dystrophin detected by Western blot.

Now, let's review the clinical evidence. As was discussed by Dr. Farkas, study 201 did not show a significant difference between boys treated with eteplirsen and those treated with placebo for the prespecified primary endpoint.

When you think of the 6-minute walk data, it's worth considering just how small the sample size is and about the fragility of the findings. So let's consider the two patients in the low-dose 30 milligram per kilo group who quickly lost their ability to ambulate.

If by chance they had been randomized to the placebo group, it is likely the trial would have shown a statistically significant difference in
favor of the drug, and the result would have been interpreted as showing a large and clinically important treatment effect based on these 12 patients.

Of course, the study did not turn out that way, but it is important to consider how easily one can be misled by a single study with a small sample size. In addition, just as study 201, study 202 did not meet its prespecified clinical endpoint.

As you heard this morning, the applicant describes highly statistically significant results in the comparison between boys treated with eteplirsen in study 201/202 and external controls, presenting a difference of 162 meters between the groups.

The applicant also describes that in a comparison of eteplirsen to external control over 4 years, only 2 of the eteplirsen treated boys lost ambulation compared to 10 of the 13 untreated external controls.

The 160 meter difference in the 6-minute walk distance, if demonstrated in an adequate and
well-controlled study, would provide evidence of effectiveness, but study 202 was not a randomized controlled trial. And several lines of evidence raise concerns that the differences in ambulation between eteplirsen treated boys and external controls are not related to a treatment effect and may be due to other factors.

As was described by Dr. Farkas, there appear to be differences between important baseline characteristics that could affect outcome in boys enrolled in the eteplirsen study compared to those of the registries.

For example, the age at initiation of steroid treatment was on average over one year earlier for eteplirsen treated patients. This difference alone could have had a significant impact on clinical outcomes.

Dr. Farkas also described evidence suggesting a differential selection of patients for the registry versus for drug studies, which leads to questions about the comparability of the groups. There may also be unrecognized and potentially very
important factors, which were not balanced by randomization, between the study and the registry cohorts.

There were apparent differences in the administration and on the performance of functional tests between eteplirsen treated boys and those of the registry. You have seen this basic figure in Dr. Farkas' presentation. Patient age is shown on the X-axis and the rise time in the Y-axis. Eteplirsen is shown in red and external control in blue.

It is striking that no boy in the Belgium or in the Italian registry had a recorded rise time greater than 22 seconds, whereas some two-thirds of eteplirsen treated boys did. Some rise times were extremely long, in some cases even greater than 40 seconds.

To be very clear, it wasn't that patients in the registries didn't experience this degree of loss of function, the point is that there is a difference, boys outside of the eteplirsen study do not contribute data for rise time greater than
22 seconds. There is a difference, but we cannot really know why there is a difference.

Perhaps the eteplirsen boys were more highly motivated, or perhaps they continued to receive encouragement from parents or staff, or perhaps the physician or the physical therapist at the Italian and Belgium sites elected not to perform testing, or to abort testing, once physical function had worsened.

Our concern is that there is an apparent difference, and it is precisely these kinds of differences, differences for known or unknown reasons, that can confound comparisons between patients in an open-label drug study and patients in an external observational cohort. And this observation is also supported by the comparison to the CINRG data as presented this morning by Dr. Farkas.

Similarly, extreme results were recorded for the 4-step climb time in some eteplirsen treated boys, but again not in registry patients. In addition, as discussed by Dr. Farkas, some boys in
the registry had recorded 10-meter run/walk results and at the same time were declared unable to ambulate, which illustrate the subjectivity in the decision to declare a boy as having lost ambulation.

These observed differences indicate that the functional test appeared to have subjective elements and that their performance may have been influenced by decisions made by the boys, the caregivers, or by study investigators. These types of differences may have a large impact on test results, and there is no way to correct for that by statistics.

Another line of evidence that calls into question interpretation of the 6-minute walk test findings comes from the inconsistencies between 6-minute walk test results and other clinical endpoints.

As displayed earlier by Dr. Farkas, the left figure shows no clear difference between eteplirsen treated boys and external controls in patterns of changes in rise time by age, with the exception of
some more extreme recorded values in eteplirsen treated boys, as we discussed earlier. And the North Star Ambulatory Assessments on the right indicate a similar decline over time for eteplirsen treated patients and external controls, with large overlap in confidence intervals through 4 years of observation.

Importantly, there is a substantial overlap of ambulation results between eteplirsen treated boys, external controls, and natural history. As was discussed by Dr. Farkas, on the right, the proportion of eteplirsen treated patients still ambulating at age 14 is not clearly different from what is expected for patients with mutation amenable to exon 51 skipping, as shown by the comparison to the Kaplan-Meier curve of loss of ambulation from the CINRG database on the left.

As we heard earlier from Dr. Temple, important issues to consider with external control trials are the possibility of bias before the trial and the possibility of bias during and after the trial. In addition, external control trials are
more likely to be persuasive when the effect is
very large and when the natural history is highly
predictable.

We have seen from the CINRG database and the
MD STARnet database that the age of loss of
ambulation spans over a decade with 25 percent of
boys with mutation amenable to exon 51 skipping
ambulatory at age 16. That variability is
problematic for a historical control study using
loss of ambulation or a 6-minute walk test as an
endpoint.

Overall, the historical control comparison
conducted by the applicant raises serious concerns
about many factors that should be considered in
interpreting a historical control study.

As Duchenne muscular dystrophy is an orphan
disease, an important issue to consider is whether
it would have been possible for the applicant to
conduct an adequate and well-controlled study. The
answer clearly is yes. This committee discussed in
November 2015 an application for another drug
developed to treat boys with mutations amenable to
 exon 51 skipping. As you remember, the application included three placebo-controlled studies, two phase 2 studies with a sample size of about 50 patients, and a phase 3 study with over 180 patients.

In the discussion at the November meeting, the committee raised major concerns about the impact of the sample size of the two phase 2 studies on their interpretability. These two phase 2 studies, which were randomized and placebo-controlled, dwarf the single eteplirsen study.

As we know, the entire eteplirsen efficacy database consists of 12 patients from a single site with a single investigator, with an open-label design, and an external control. While there is no specific minimum number of patients that should be studied to establish effectiveness of a treatment for any rare disease, the number of patients must be sufficient to draw scientific conclusions, taking into account the study design and the study outcome measures.
This afternoon, you will discuss whether evidence has been presented to you to support approval based on a biomarker reasonably likely to predict clinical benefit or based on a clinical endpoint.

It is important to keep in mind that the difference between accelerated and full approval is the type of endpoint and not the strength of the evidence. As was discussed by Dr. Dunn, substantial evidence is required for both pathways, and accelerated approval cannot be used to compensate for weak or inconsistent clinical findings.

Now, I would like to speak directly to the study participants and their families. I want to thank you for your extraordinary commitment and efforts to the incredibly important endeavor to make a new drug available for the treatment of Duchenne muscular dystrophy. I do understand your situation. You have a devastating disease, and you have placed great hope that this experimental treatment will change the course of your disease.
I understand your fight because it has been my family's fight. I have a sister who is profoundly disabled since birth, and who almost did not make it through her first days of life. My parents spent considerable time and resources to get her access to experimental treatments.

My parents would have done anything, anything to create a brighter future for my sister, and I would do the same for my children. And a number of my close collaborators, some in this room, are facing similar situations.

But my role here today as a member of the neurology review division is very different. My role, regardless of the pressure that has been placed on my division, and in particular on the eteplirsen review team, is to present our scientific review and conclusions about eteplirsen.

We are a science-based organization. That review has been very careful. Really, it has been exhaustive, and has involved a large multidisciplinary team of reviewers. Even though just a few us are talking to you this morning, I
want to assure you that nothing that was presented today represent the unique view of a single reviewer. Instead, it is the product of a large team effort with considerable oversight and feedback by all levels of FDA management.

We are looking forward to your testimony this afternoon, and I'm looking forward to a good and productive discussion with the members of the advisory committee. Thank you.

**Clarifying Questions**

DR. ALEXANDER: Thank you, Dr. Bastings.

We now have 15 minutes for questions, clarifying questions for the FDA. Again, please remember to state your name for the record before you speak. And if you can, please direct your questions to a specific presenter.

I'll take the prerogative as chair to ask a first question, which is clarifying the selection of the controls from the CINRG study. There was some concern raised on the part of the sponsor, if I understood correctly, regarding the way that the controls were selected and that the individuals
that were selected may have represented outliers.

So I'm wondering, from the FDA, if someone could speak to how these controls were selected. And in particular, I'm interested in whether there were sensitivity analyses performed using different criteria to select different control groups from the CINRG study, that is, is there an opportunity to look at how the conclusions that one reaches differ based on the control patients selected from CINRG.

DR. FARKAS: It's Ron Farkas. Well, let me start. One thing is actually in my mind, it's not exactly clear to me what the issue -- or what the concern was that was raised, but I can describe how we picked the controls. And that was being very careful to separate -- so the review division didn't take a look at any of the data. We took a look at some of the baseline characteristics of the patients without knowing their course, and then matched patients that were similar just on those baseline characteristics, and then the statisticians conducted these comparisons.
So there were no — I mean, on purpose, there were no multiple looks, no sensitivity analyses. It was pick some patients that looked similar. And again, it was not close matching. I think that's something that's important to understand, too. We tried close matching. We actually wrote out a detailed protocol to do close matching, but there weren't any matches, and so we relaxed and relaxed and relaxed until it just seemed like there was kind of some similar baseline characteristics and had the statisticians then do the calculations.

DR. ALEXANDER: Thank you. Dr. Ovbiagele?

DR. OVBIAGELE: Bruce Ovbiagele. My question is for Dr. Farkas.

DR. ALEXANDER: Can you speak into the microphone a little more, please?

DR. OVBIAGELE: Sure, sure. My question is for Dr. Farkas. Of course, when you look at the different prognosticators, the big differences you see already with the steroid treatment. And as you might remember from page 39 of the applicant's
presentation, the two issues were the age at
steroid start, and the other issue was continuous
treatment with steroids, which was much, much
higher in the eteplirsen group.

The applicant looked at the effect of
continuous treatment in the external control group
and found there was no significant difference. Did
you look to see if there was a difference in terms
of age at steroid start, in terms of its effect on
the outcome?

DR. FARKAS: Right. I think that there was
a difference in the age at steroid start. But
going back to the daily versus every other day
treatment, I think one of the concerns that we have
is that it didn't seem like the data was reliable
for the daily versus every other day.

The NDA came in. We took a look at the
counts for daily versus every other day. We raised
some concern about that. And then we heard later
from the applicant that the data was incorrect as
submitted, in that there were more patients on
every other day treatment in the historical
controls than had been originally reported, which raised some definite concerns in our mind when the data seems to change or wasn't really certain.

With regard to seeing if there's a correlation between the treatment given and the clinical course, I think at some point -- I think we tried to be careful to point out that, you know, lack of a correlation between low levels of dystrophin and how patients did on clinical course, it's so very underpowered. And then for some of these other comparisons, we're dividing the patients in half again.

So it's true. There wasn't a correlation shown there, but if it's comparing four patients to four other patients, I'm not sure what we can really see.

But again, I think that the main point that I tried to make in the original version of the memo that I wrote, and even later on, is that it isn't necessarily large differences that might account for differences in clinical course. I mean, the whole issue that's been identified by experts in
DMD is that things that seem small can confound differences between groups.

DR. OVBIAGELE: No, I recognize that, but I think the issue of course is that since that of course is one of the issues that has been raised as potentially problematic, at the very least, it might be somewhat reassuring if there was no impact of age of steroid start on the actual clinical outcome in the external control group, if you see what I mean.

DR. FARKAS: Yes. I'm just not sure that you can -- so on one particular factor, you can see that very small groups of patients don't divide from each other. But I'm not really sure how much reassurance that gives that the differences couldn't have resulted in a changing clinical course.

Of course, but backing up, I mean, in some sense I regret that almost that I brought this up --

(Laughter.)

DR. FARKAS: -- because the sources of
difference between the patients is so large in so many other respects. It was a true point the differences in care can lead to differences in clinical outcome, but it's overshadowed by I think other issues.

DR. ALEXANDER: Thank you. Dr. Bastings and then Dr. Hoffman.

DR. BASTINGS: Yes, listen. What we know is that patients in the registries started the steroids over one year earlier. The cohort size is just too small to look for any correlation with outcomes, but it's a fact that steroid treatment is effective and widely used in Duchenne muscular dystrophy, and the effect of initiating earlier cannot be overstated.

Yes, yes. I'm sorry, I said it backwards. The eteplirsen patients started earlier. Okay.

DR. ALEXANDER: Thank you. So the eteplirsen patients started on average one year earlier, started steroids.

DR. BASTINGS: Over one year earlier.

DR. ALEXANDER: Thank you. Dr. Hoffman?
DR. HOFFMAN: Richard Hoffman. I just have a general question. It appears that the FDA is suggesting that another placebo-controlled trial will be needed. And I was wondering if eteplirsen is granted accelerated approval, would a future placebo-controlled trial ever be possible?

DR. ALEXANDER: Who is that a question for?

DR. HOFFMAN: Anybody in the FDA.

DR. ALEXANDER: And when you say possible, are you speaking --

DR. HOFFMAN: Well, once it receives accelerated approval, it would be available to all patients, and what patients would want to be a placebo patient at that point?

DR. BASTINGS: I think this is a very good question. It seems unlikely that if the drug becomes accessible to patients, that anybody would enroll in a future study that is placebo-controlled.

DR. ALEXANDER: Dr. Jenkins?

DR. JENKINS: Yes, this is John Jenkins. To help address that question, if you recall the
applicant stated their trials are ongoing or
planned that they consider to be confirmatory.
They had some externally controlled trials for
eteplirsen in exon 51 amenable patients. They also
had a couple of trials in two other exons that are
placebo-controlled hoping that if they can show a
significant difference in those placebo-controlled
trials in other exons, it would help to validate
the findings for eteplirsen.

So their confirmatory trials are externally
controlled for eteplirsen, placebo-controlled for
two other exon-skipping patient populations. But I
think you raise a good point about -- anytime a
product is approved under accelerated approval, or
any type of approval, the question of whether you
can then do a trial that's placebo-controlled
becomes very challenging, particularly in serious
and life-threatening diseases where patients may
not be willing to be on placebo.

DR. ALEXANDER: Thank you. Dr. Onyike and
then Dr. Gordon.

DR. ONYIKE: Thank you. Chiadi Onyike.
Now, I'd just like to take attention to slide 72, if we could pull that up please. Slide 72. And, yes, acknowledging -- this is for Dr. Farkas. Acknowledging that you've looked at converting multiple levels of evidence and converging outcomes, especially on the clinical side, I just wanted to explore for a minute the subset of subjects in the treatment group who seem to have function -- I mean preserved walking, so the ones that are encircled.

I just wondered if you had a way -- I know that most of the comparisons that are done with respect to the two groups are based on a visual analysis, at least the way you presented it, on a visual analysis of the trajectories of the slopes.

I just wondered if you had some way to quantitatively analyze the trajectories of those slopes and to compare them. And the reason I say that is because your analysis of any extrapolation as to what might be the future of these subjects was based on other sources of data as opposed to direct comparisons. So I just wondered if you were
able to do that.

DR. FARKAS: Yes, well I guess the first thing, or to pick up on the last part of what you said, is that everything is external, all the comparisons are external. So this was one group of patients that were selected by the applicant, and other sources of information were basically available at the same time.

Part of the issue is -- I mean, the FDA had asked for comparison to multiple sets of data, all the data that might be available. So there is no primary comparison to one historical group versus another historical group.

But as to your question of numerical comparisons, I think that's an important point, but that's not the way we can analyze studies like this. This is just the truth about historically controlled trials. There's not really going to be an answer in the numbers because we have to account for these other sources of differences between the groups.

So one of the key pieces of advice that we
give to people is that if there's the opportunity for doing a historically controlled trial for sponsors, but that unless there's a clear difference, kind of an obvious difference, is the answer in the end between the treated patients and the controls, it wouldn't be possible normally to conclude that it was an effect of the drug and not other differences between the patients and the way the study was conducted.

DR. ALEXANDER: I'd like to wait one minute, please, for Dr. Gordon and just go to Dr. Romitti if we can, and then we'll come to Dr. Gordon at the close of this section.

DR. ROMITTI: Okay. Paul Romitti. So there has been discussion by both the applicant and the FDA about dialogue that's gone back and forth. And in going through the materials and trying to construct my own timeline of all these dialogues, it's just unclear to me when this recommendation from slide 50 of Dr. Farkas' slides was first given.

So that slide, as you see there, says the
FDA consistently and strongly encouraged the applicant to perform a randomized double-blind control trial. Can you give us the month and the year that recommendation was first made?

DR. FARKAS: Well, I mean I have the month and the year somewhere. It's not right in my head. But I would be able to say that -- so the applicant conducted an analysis at about week 48 in the original study 201 and presented those analyses to us in late 2012 or 2013.

We were very much concerned that their analysis was not supportable, not scientifically supportable, and were giving them very strong feedback from that point that we thought that would not be convincing data.

DR. ALEXANDER: Dr. Bastings?

DR. BASTINGS: I think Dr. Dunn has the exact date. Maybe he does. This has been stated on multiple occasions, not just one time, on multiple occasions. Dr. Dunn?

DR. DUNN: I have one exact date for you. Keeping in mind that 1, 2, 3, 4, 5, at least 6
people in a row here have said, more times than I can count individually to the sponsor, you need to do that. The date that's in front of me right here from Dr. Breder, the primary reviewer of this application, mentions the importance of conducting a placebo-controlled design using multiple fixed doses in phase 3 development, on June 14th of 2011.

DR. ROMITTI: Thank you.

DR. ALEXANDER: Thank you.

Dr. Cohen [sic], final question for this section? I'm sorry, Dr. Gordon.

DR. GORDON: This is Mark Gordon, industry representative. So to follow up on the comments from Dr. Farkas and Dr. Bastings, both of you mentioned that the inability to perform the 6-minute walk test was an important determinant in the loss of ambulation.

You also mentioned that there was some level or element of a subjective component that possibly influenced the function. So my question is both in the sponsor's study and in CINRG, was there any protocol defined definition of the inability to
perform the 6-minute walk test?

DR. FARKAS: That's an important point. And the protocols from the natural history study were extremely brief, and they didn't specify anything; extremely brief, just several pages.

The protocol for the CINRG study is very detailed. It does make mention of a 25-second cutoff for the 10-meter run/walk, but it doesn't specify very clearly actually how or when endpoints will be measured. And I mean we have, you know, Dr. McDonald here, and he's been extremely helpful to the FDA, and we've discussed on the phone with his collaborators.

To our understanding, it is a subjective discussion the patients and the parents and the investigators do decide at the study visits what test the patient will attempt and which they won't.

DR. ALEXANDER: Thank you. I'd like to give the sponsor a chance to respond either or both to that question and any other very brief responses to questions that have been raised, and then we'll move to the open public hearing.
MS. RUFF: Thank you very much. We have Dr. McDonald here, who will answer a question about the choice or the decision about 6-minute walk test and loss in ambulation. And then Dr. Kaye would like to just address a comment about when FDA told us about placebo-controlled studies.

DR. MCDONALD: My name is Dr. Craig McDonald. I'm director of neuromuscular disease clinics at University of California Davis. And I'm the study chair of the CINRG Duchenne Natural History study. I've been compensated by Sarepta Therapeutics for my time, and I have no direct financial interest in the outcome of today's meeting.

I would like to make some a few very important clarifying points here with regard to the definition of loss of ambulation. If I could have the first slide up.

The CINRG has a very specific definition of loss of ambulation. We've published multiple studies in peer reviewed journals based on this definition. It's based on a physician assessment,
patient and parent report a full-time wheelchair use on a standard CRF, so there's no independent household ambulation or minimal ambulation.

This is, when available, corroborated by the loss of the ability to perform the 10-meter walk/run test. That's a very different definition and standard than what I think the sponsor appropriately used in this trial. If I could have the next slide up.

The sponsor defines the loss of ambulation as the acquisition of a 6-minute walk distance of zero. And what you see on the left is actually the worldwide available literature on 6-minute walk distance that has been obtained both in placebo arms as well as registries.

The data on the right is actually published registry information from Goemans. What's really quite dramatic here is you see that the data is almost superimposable in terms of that obtained by natural history studies and that obtained in placebo-controlled arms of studies.

So this really I think addresses the concern
about motivational aspects or biases, where we're seeing very similar data. The most important point here is if you look at this definition of loss of ambulation, virtually only about 2 to 3 percent of patients, based on a 6-minute walk distance definition, continue ambulating past the age of 15. If I could have the next slide. This was the CINRG data that was discussed by the sponsor as well as by Dr. Farkas. And what we see here is the patients from the CINRG cohort exon 51 mutations, the 25 percent of patients that Dr. Farkas alluded to there, that's based on a CINRG definition of inability to perform the 6-minute walk test as well as physician and patient determination of full-time wheelchair use.

I should point out that this is rather limited data set. It only represents 3 patients, that when you talk about 25 percent, that only represents 3 patients. And what we see in the blue line there is something very different I think with the eteplirsen treated patients. We're seeing, first of all, those patients haven't reached the
age of 16 yet. But what we see is 10 of
12 patients still walking based on rigorous
definition of 6-minute walk distance as the
definition.

If I could just finish by focusing on rise
time, as this has been something that has been an
important point made by the FDA. If I could have
the next slide up.

So rise time and rise ability is really an
important prognostic endpoint. If I could have the
next slide up. And I think it's important to point
out here, there's a matter of definitions. The FDA
focuses on the absolute time taken to perform the
test. The sponsor, on the other hand, really
focuses on the critical importance of the loss of
this endpoint in terms of independent ability to
perform the test.

So the loss of this endpoint as we know it
is really what's prognostic. And this is CINRG
data here. If we could pull up the slide actually
on this screen. Slide up, please.

This is actually CINRG data on rise ability
and loss of rise ability and its prognostic
importance for loss of ability to ambulate. And
what you see here actually in the CINRG data is
it's not the absolute value of rise time that's of
prognostic value, it's the loss of the rise
ability.

So what you see there in the red are those
patients who have completely lost the ability to
rise independently. And virtually 50 percent of
those patients have lost the ability to ambulate
within 12 months. And in fact, 70 percent of those
patients lose the ability to ambulate at 24 months.

If you look at purple and blue lines at the
top, that shows the survival curves when rise time
is less than 5 seconds, 5 to 10 seconds, or greater
than 10 seconds. The actual rise time is not a
prognostic value. The importance is the loss of
rise ability independently.

If we could just show the next slide, this
shows how the sponsor has actually focused on loss
of rise ability independently. And what you see
there is 3 years out a high percentage of
eteplirsen treated patients have maintained the rise ability, a very small percentage of the external controls. But I think what's even more striking is when you look at years 1, 2 and 3, the patients that have lost rise ability have still maintained the ability to ambulate over a prolonged period of time. Thank you.

DR. ALEXANDER: Thank you very much. I do want to move on to the portion of the open public hearing.

(Applause.)

DR. ALEXANDER: Thank you very much.

Dr. Bastings, and then we'll move on to the open public hearing.

DR. BASTINGS: I would like the applicant to bring back the slide comparing the Kaplan-Meier curve from the eteplirsen patients to the CINRG database that they just showed.

DR. ALEXANDER: Can the sponsor please project that slide?

DR. BASTINGS: Yes. I would like to point out that that slide is totally misleading, because
most of the eteplirsen patients shown in blue here have not reached the age 15. So there is just no way to make that sort of comparison because they simply have not reached that age yet.

Open Public Hearing

DR. ALEXANDER: Thank you. We will have more time for discussion during the question period after the open public hearing.

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 open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you 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 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 comment 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 concluded in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.
Will speaker number 1 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. FITZPATRICK: Good afternoon, and thank you for allowing me --

DR. ALEXANDER: Can you please speak a little more directly into the microphone? Microphone on, please. We need audio at the podium.

MR. FITZPATRICK: Good afternoon, and thank you for the opportunity to address the advisory panel this afternoon. My name is Mike Fitzpatrick. I represent the 8th Congressional District of Pennsylvania.

I want to begin by thanking you for holding this hearing, as well as for the agency's ongoing commitment to use its full range of tools and authorities to expeditiously review candidate therapies for rare but devastating diseases, like Duchenne muscular dystrophy.

I'm a member of the Congressional Rare
Disease Caucus, and I've discussed and advocated for funding and research opportunities for a number of medical conditions, many of which have connections to my district in Bucks County, Pennsylvania.

That connection for Duchenne muscular dystrophy is 15-year-old Jake Wesley, who suffers from this terrible disease. Sadly, like so many in Jake's position, the decline of his health has been precipitous. The risk of doing nothing for someone like Jake is unacceptable. I've seen his disease progress year after year, robbing him along the way of any sense of his own independence, and Jake deserves better.

There is a path forward, one which could alter the lives of all Duchenne patients in a very positive way, giving them a chance to live a longer, better life. As you know, in recent years the Congress along with the FDA have made tremendous progress toward, through the Food and Drug Administration Safety and Innovation Act, providing new therapies intended to treat persons
with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists, in this case Duchenne.

The accelerated approval pathway outlined in Section 901 of the Act, allows demonstrably safe therapies that treat an unmet medical need, and appear to be efficacious, even with some uncertainty, to avoid the years of regulatory barriers and become accessible earlier to patients who otherwise have no other option.

FDA has been most successful at applying flexibility in oncology and HIV/AIDS to speed patient access to apparently safe treatments, but the need and the opportunity to adopt innovative and flexible approaches to the review of rare disease drugs has never been greater than it is today. Children like Jake are waiting.

That is why today my urgent call is echoed by 108 other bipartisan members of Congress who have joined me in writing to Dr. Janet Woodcock, and I would ask, with the panel's permission, that this letter, signed by 108 of my colleagues, be
entered as a part of this record today.

I remain committed to ensuring --

(Applause.)

MR. FITZPATRICK: -- and it's difficult to get 108 of my colleagues to agree -- [mic off].

DR. ALEXANDER: Thank you very much.

(Applause.)

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

MS. JURACK: Yes. Good afternoon, committee. My name is Karen Jurack, and I have not been financially compensated by anyone to be here today. I am the mother of a soon to be 15-year-old. His name is Joshua. He has been battling Duchenne muscular dystrophy for 10 years now. He was diagnosed at 4 and a half with a deletion mutation in genes 49 and 50, making him a perfect candidate for exon 51 skipping therapies.

Joshua lost his ability to walk at age 9, had spinal fusion surgery at age 13, and since the
surgery Joshua has lost a great deal of his arm mobility. He can no longer feed himself, which is a distressing loss of independence.

As a parent, it's very difficult to watch your child continue to get weaker every day. You feel absolutely helpless, and you never believe you're doing enough to help your child get better. Because steroids alone are not sufficient, I constantly check the availability of clinical trials for Joshua. And unfortunately, in the majority of cases, he did not qualify for those studies because he has not been ambulatory for several years.

When I found the Sarepta eteplirsen study, I was delighted because the study parameters were such that we could potentially qualify. In March 2015, Joshua and I went to Johns Hopkins and tried to take part in this trial, however he was excluded because he could not lift a glass of water to his mouth. We were devastated by this news.

In the fall of 2015, as part of their medical training, Joshua was interviewed by some
medical students. One of the questions he was asked was what he worries most about for the future. I fully expected him to say college, but very calmly and soberly said he was worried most about his lungs and heart failing him. This shows the reality in which he lives, the thoughts of his mortality that totally consume his every being.

Joshua has a brilliant mind, however he is trapped in a body that doesn't work. He's always been an exceptional child. He's an overachiever in academics, scouting life, and unfortunately with Duchenne. Joshua's muscular dystrophy seems to be progressing at a faster rate than most of his peers. Now more than ever time is of the essence for our family.

Despite his physical decline, Joshua remains optimistic and determined to meet his goals in life. For example, he'll be completing his Eagle Scout service project this coming Saturday.

Although Joshua was not included in the trial for eteplirsen, we would welcome the opportunity to have access to this drug therapy.
For Joshua, success would include gaining some strength in his arms where he could once again feed himself and not be secluded from others during school lunch. If there's the slightest chance exon skipping could improve and prolong his quality of life, we would be thrilled with the prospect.

Exon skipping therapies offer our family and many like ours a tangible hope that a viable option for slowing the progression of Duchenne is at hand. With exon 51 skipping therapies, Joshua's future may become more of a reality. Thank you for your time.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 3 please come to the podium and introduce yourself. Please state your name and any organization you are representing for the record.

MR. BASILE: My name is Carlo Basile, and Make Duchenne History Coalition paid for my trip today to be here. I thank you for the opportunity to speak today. Again, my name is Carlo Basile. I'm chief secretary to Massachusetts Governor
Baker. He wants everyone in the Duchenne family to know he stands behind us.

As one public servant to another, I want to remind you that your job's here to serve the people. But before that, before I go on -- and everything I say is as a parent and not as the governor's chief secretary -- I find it insulting that someone would tell me or these people behind me that you understand. Unless you have a child that has muscular dystrophy, you don't understand.

Today, your job is to serve all Americans who are living with Duchenne, have lost one to Duchenne, or yet to be diagnosed or born with Duchenne. To help inform your deliberations, I would like to make two important points lacking in the FDA's framing of the vote questions. These points are important to ensuring you should uphold the integrity of the vote process.

First, the FDA states in framing the vote questions that, quote, "The intent of the statutory requirements is to reduce the chance of incorrect conclusion that a drug is effective when in fact it
is not effective."

Earlier today, Christine McSherry mentioned this is type 1 error. I'm disappointed that there is no similar mention in FDA's briefing materials about type 2 errors, where the FDA fails or delays approval of a drug that is in fact effective. I would like the FDA to address after the open public hearing how they are accounting for type 2 errors today.

Every day with my son, I witness the human costs would be making type 2 error Duchenne in the Duchenne population. In the past year alone, Carlo Jr. has followed the natural history of Duchenne and lost the ability to carry his backpack, run with his brother at a natural speed, bouncing a basketball, amongst other things. And the next three years, I don't even want to imagine what he'll be facing.

My second point is, the FDA emphasizes upholding statutory standards of approval. Yes, a drug must demonstrate effectiveness to be approved. But according to the regulations, the FDA also must
apply the broadest flexibility in applying the statutory standards for the drugs that treat life-threatening, severely debilitating diseases, especially where no alternative therapy exists.

Just the context, the Congress passed the FDASIA 2 -- [mic off].

DR. ALEXANDER: Thank you very much for your comments.

(Applause.)

DR. ALEXANDER: And I'd like to ask if everyone would mind holding their applause until the end. We have about 52 speakers that we'll be hearing from and would just request that you hold your applause until the final speaker. The next speaker is speaker number 4. If you could please come to the podium and state your name and any organization that you're representing for the record.

MS. MINER: My name is Malanie Miner. My travel was paid for by Make Duchenne History Coalition. My 17-year-old son, Cobi, has Duchenne. By the time Cobi was 3 years old, we had a feeling
something just wasn't quite right. By the time he was 5, we got a diagnosis of Duchenne.

During a visit to Cincinnati Children's Hospital in 2011, we were told that Cobi could be a candidate for a new drug trial, the same trial that is under review today. An initial pre-screening showed that he met all of the strict requirements for this trial. At this time, Cobi was ambulatory and relatively healthy for an 11-year-old with Duchenne.

Unfortunately, there was a delay in the start of the trial, and by the time Cobi was screened in July of 2011, at age 11, his baseline walk test had declined so much that he no longer met the study's strict trial criteria. We were devastated by the decline at only 11 years old.

Cobi broke his leg soon after and never walked again. It is very bittersweet for me to be here and see the boys who have been on eteplirsen since 2011 and compare them to my son. Five years ago, Cobi was just like them, but now the difference is stark and painful.
A few weeks ago, Cobi contracted pneumonia. He suffered from septic shock. During a prolonged stay in the ICU, we heard more devastating news. Cobi is now in heart failure.

In their briefing documents, FDA states that the loss of ambulation ranges from 8 to 18 years old. This is not what I see in the hundreds of people I know in the Duchenne community. There are a lot of 9 and 10-year-olds with Duchenne dying, yet there was no mention of that in the briefing documents.

There are a lot more boys like Cobi who have Duchenne dying in their late teens than there are ones walking until their late teens, as described in the FDA's briefing documents. My son is the true placebo and a true natural history of Duchenne, the eteplirsen boys are not.

In summary, Cobi would be with us today, but because of his heart failure he could not attend. And if eteplirsen is approved, I believe that it could still help Cobi. If he had access to it, it could still potentially improve and prolong his
life.

(Applause.)

DR. ALEXANDER: Thank you for sharing your experience. Will speaker number 5 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. McSHERRY: Thank you, Melanie.

This is Christine McSherry. Jett Foundation and Make Duchenne History Coalition provided the funds for my travel this morning. Just to get to Dr. Bastings point, I just want to remind FDA and the panel that one of the reasons why the parents came to you before the data was presented is because we saw those signs that the drug was working, and therefore a placebo-controlled trial would be not feasible. I just wanted to make the comment.

But I'd like to talk to you today as mother and advocate. You did hear from me this morning in the Patient Reported Outcome project. My son Jett was diagnosed when he was 5, today he's 20. Jett
took his last steps at the age of 13 despite being on 40 milligrams of daily deflazacort. It's a high dose. Last year, Jett enrolled in a limited ambulation safety study for eteplirsen, and in my view, he has stabilized and some things have gotten better, and you've heard about those things.

But that's not what I'm here to talk to you about today. I want to make sure that the panel understands what all of us are advocating for. We're asking the FDA to approve a drug that's demonstrated consistently efficacy on multiple measures.

We're asking that the agency utilize flexibility in the tools it has to approve a remarkably safe drug while pursuing confirmatory trials. If as a result of those trials, it becomes clear that eteplirsen is not working, we will stand behind the agency should it decide to remove it from the market. You see, we only want drugs that work.

We're not asking the FDA to lower its standards or grant wishes to a desperate community.
We are a community that is well-informed, a community that funds and drives research, a community that writes draft guidance for drug development. We are here in large numbers because eteplirsen has met the safety and effectiveness standards for accelerated approval.

As a mother and an advocate, I'm surprised and disappointed by the briefing documents released in January, even more so by those released last week. What's clear from those documents is that the Division of Neurology is seeking to send a message to Sarepta, industry, and the rare disease community; a message that we will only accept a large randomized, double-blind, placebo-controlled trial, no matter what the severity or the disease.

We were very encouraged when FDA issued the DMD draft guidance, which included historically controlled data as a potential pathway for approval. Now to see the FDA distancing itself so aggressively from that guidance is extremely disheartening.

If FDA really wanted a large placebo-
controlled trial, why did the neurology division
guide the company to start a single-arm study in
the 4 to 6-year-olds who would age into that study?
There's virtually no one left who is drug naïve to
enter into such a trial. We expect the FDA to
provide clear, viable regulatory pathways towards
approval. The goal post cannot be changed.

Twenty-five years ago, FDA utilized
accelerated approval to save a generation of young
men dying of AIDS. Today the agency has another
generation of young men that they could also save
from Duchenne. It's time for the neurology
division to join oncology and the anti-viral
divisions, among others, follow [mic off].

(Applause.)

DR. ALEXANDER: Thank you. Will speaker
number 6 please come to the podium and introduce
yourself? Please state your name and any
organization you are representing for the record.

MR. WILLIAMS: My name is Brady Williams.
My friend, Bryson Foster, a former NBA goodwill
ambassador, said if we can find a cure, we can save
people's lives. We have not found a cure, but we are saving lives with this drug. The average boy stops walking with DMD around 10 years old, but I am still going strong, nearly 15 years old.

MS. WILLIAMS: My name is Martha Williams, and the Make Duchenne History Coalition arranged for our travel. This is my son Brady standing here with me today. He walked in at 14 years and 11 months old. He's still able to walk independently, other than long distances, and that's quite an accomplishment for any boy Brady's age with Duchenne muscular dystrophy.

Brady's steroid usage has only changed once in the 9 and a half years that he's been on it. The change was simply due to the recommended dosage for his weight, and he's still under-dosed for his weight. He's been off and on physical therapy with many extended breaks.

The therapy consists of 1 to 2 times a week, in the pool and on land, and there's been times that we've had a break or more from therapy. At home we do some stretches, and he wears night
splints a few nights a week, but this is the
typical regimen for a boy with DMD, and this is by
no means to be considered an intense treatment.

Although Brady still falls on occasion,
these falls have gone from almost a daily
occurrence to 1 to 2 times a month. It's a relief
to know that we don't have to fear a fall every
time he's out of our sight. At MDA camp, Brady is
one of the only boys in his age range with Duchenne
muscular dystrophy still able to walk.

He can get out of the pool and jump in from
the side independently. He can keep his head above
water for 10 minutes at a time, and before he was
on the medication, he would sink immediately below
the water because he didn't have enough strength in
his neck to hold himself up.

Brady's lung function continues to be good,
and his heart is functioning normally, which was
confirmed with his recent cardiac MRI. Although
Brady's ability to walk is reassuring us that this
treatment is working as intended, him having good
lung and heart function is more than we could hope
for at his age with this disease.

Brady has been infused weekly for 5 and a half years without missing one single dose. Other than the occasional bruise, which would be expected with any needle, he has had zero side effects from this medication.

We have no doubt without the treatment, Brady would have been confined to a wheelchair full time, and we would not see the heart and lung function he has from being in this trial. This medication is safe, it's effective, it's working.

Brady along with these other boys have endured more than most do in a lifetime. The approval of this medicine is essential to ensure his continued stabilization for his heart and lungs and reduce the overall decline for him and the others afflicted with Duchenne muscular dystrophy.

Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Once again, please hold your applause until the final speaker has spoken.
Will speakers number 7 please come to the podium and introduce yourselves? Please state your names and any organization you're representing for the record.

MR. DUNNE: My name is Chris Dunne. My wife and I are the parents of Ryan, a 12-year-old boy who was born with Duchenne muscular dystrophy. Being a parent of a child with DMD means that there are a lot of milestones ahead. In the not too distant future, Ryan will lose the ability to walk and will be forced to rely on a wheelchair.

After that, Ryan will lose the ability to go to the bathroom on his own, and then he will not be able to feed himself. Finally, he will lose the ability to breathe on his own, and he will die before he has a chance to truly live.

Those are just a few challenges that Ryan has to look forward to. He already has to live with the fact that he cannot play with his peers, that he has to struggle in school, that as a fifth grader he is smaller than most second graders because he has to take steroids all of his life.
In 2014, Ryan had the opportunity to become part of the eteplirsen trial. We jumped at the chance. Ryan did not jump because he had lost the ability when he was 9. Ryan's been receiving eteplirsen for 72 weeks without any adverse events or side effects. Time has always been the worst enemy of children with DMD. Eteplirsen has however given us a reason to hope.

The people who see Ryan daily, teachers, therapists, friends and family, notice that things are better, less falls, more stamina, greater strength, and even a regained ability to jump. All this on a steroid dosage that is less than half of the standard 0.9 milligrams per kilogram.

Not a single person here believes that eteplirsen is the cure for DMD, but no one can deny that it is a valuable treatment. Eteplirsen is as important to boys with DMD as insulin is for diabetics. We know what will happen if our children are denied this life-saving medicine, a steady downward progression ending in an untimely death. You can change that today.
MR. PASCHAL: Hello. My name is Kris Paschal, and I am a father of a 13-year-old boy, Samuel, with Duchenne muscular dystrophy. Our son Sam and our family moved to England in 2011 because we didn't have much faith in the FDA's ability to take up orphan drugs, and thought the best opportunity would be in Europe where Sam participated in the drisapersen trial. We have since repatriated and become a part of the eteplirsen trial.

The difference between the two have and night and day in efficacy. Sam had no less than 6 times when the protein in his urine on the other drug was elevated. He has never had that since we've been on eteplirsen, so the efficacy is night and day.

I'd like to remark that this morning, we spoke of the law behind this, and I think Estes Kefauver and Oren Harris would be appalled at the process we are going through. It was meant to protect the consumer who was uneducated from the
unscrupulous drug companies. I think today we have
clear evidence that we have an educated consumer
here who is asking that you seriously consider this
given the merits of the drug.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker number 8 please come to the podium and
introduce yourself? Please state your name and any
organization you are representing for the record.

DR. FLETCHER: My name is Sue Fletcher. I'm
a researcher with Murdoch University in Australia.
We pioneered PMOs for exon skipping and developed
the eteplirsen sequence license to Sarepta, I
therefore have a financial interest in the outcomes
of today. I am also a consultant to Sarepta.

In this presentation, I comment on three
issues: the validity of Western blot to assess
dystrophin expression, how much dystrophin is
normal, and lessons learned from the mdx mouse.
Western blotting is a useful technique for
assessing protein quantity and quality and
comparing between samples within a study.
At this time, no universal dystrophin reference standard is available, and therefore, each study must stand alone and be accompanied by valid reference standards. This means that we cannot equate dystrophin expression in one study with data from another that uses a difference reference and different protocols.

Dystrophin levels cited in Duchenne and Becker are mostly from early reports relying on technologies not consistent with accurate quantitation. If signals from the test and reference samples do not all lie within the linear range, quantitation is not possible.

A black image band from a blot means pixels are saturated, and therefore using current technology are interpreted as infinity. I present a blot showing muscle protein expression in non-dystrophin subjects; dystrophin in samples D and E differ by approximately 9-fold. It is obvious that such a broad range in dystrophin levels would have implications for the analysis of de novo dystrophin expression in samples.
The dystrophin Western blot data presented by Sarepta demonstrates greater scientific rigor than is evident in any other published reports I have studied. Dystrophin expression in untreated DMD muscle is reported as average 0.08 percent relative to the reference sample used, and that in muscle from treated patients 11-fold higher.

Use of a different reference sample and/or protocol would deliver different numbers, but it is the increase in dystrophin expression after eteplirsen treatment that is the important outcome. If the 180-week dystrophin analysis of 0.9 was relative to the higher dystrophin on our immunoblot, that is sample E, then comparison to sample E would yield a figure of 8.1 percent. I use this data to illustrate it is not the actual number that is important, it is the increase in dystrophin after treatment.

My extensive experience as a scientist working on mdx mice has yielded key findings relevant to the discussion today. Systemic PMO 23 treatment in mdx mouse induces de novo dystrophin
in all muscles, which correlates with improved function. PMO M23 [ph] treatment initiated in newborn mice prevents the onset of dystrophin pathology.

In closing, based on all our research and the data presented by Sarepta, it is evident that eteplirsen induces de novo dystrophin expression. I believe that it is reasonable to conclude that the increase in dystrophin is responsible for the clinical benefit reported in the patients. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 9 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BYRNE: Mr. Chairman and the committee, my name is Barry Byrne. I'm a clinician scientist with experience caring for boys with Duchenne muscular dystrophy as a pediatric cardiologist.

I'm a member of the FDA committee on cellular tissue and gene therapies advising CBER,
and I have no financial interest in the outcome of this meeting. I've served as a scientific advisor to Sarepta, and our center is a hub site for the PROMOVI phase 3 study. Most importantly for the discussion today, I am privileged to care for one of the patients in the 201/202 study who is here to share their experience as a participant of the pivotal eteplirsen study under review.

My objective in these brief comments is to draw a parallel between the study of eteplirsen and a related pivotal study leading to the marketing approval of Myozyme for Pompe disease. Our center was the lead enrolling site of the Myozyme studies, and I think a comparison to this small study using historical cohort is relevant to the discussion today.

The primary endpoint of the Myozyme study was ventilator-free survival. The secondary endpoint of overall survival was compared to an only 2 percent survival rate in the historical cohort. Based on the comparison to this historical cohort, Myozyme was approved for commercial use.
when the initial findings showed overall improved survival. After 4 years of treatment, 44 percent, or 7 of the 16 subjects were alive without assisted inhalation.

In comparison, the clinical endpoint of functional ambulation is an equally critical important endpoint in Duchenne. The importance of this type of binary endpoint is often emphasized by the agency and experts in the field. I think that the finding of 83 percent of eteplirsen study participants who are ambulant after 4 years to therapy compared to the finding of 44 percent survival in the Myozyme study should not be overlooked.

Movement and freedom of ambulation is really life sustaining for a boy with Duchenne, and the open-label Pompe studies relied on historical cohorts since we accept that pediatric studies require a prospect for direct benefit, therefore prohibiting a contemporary placebo control.

So I think Sarepta has designed and conducted the 201/202 studies with these important
principles in mind, and they've been diligent as a sponsor of the studies under consideration today. Although this is a small study, the effect is in fact well controlled given the constraints of pediatric rare disease research. And based on these observations of my patient in the study and in the light of the findings today, I strongly believe eteplirsen meets the standard for substantial evidence of effectiveness and warrants approval in boys with Duchenne muscular dystrophy.

Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 10 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GOTTSCHALK: Hi, I'm Dr. Laura Gottschalk speaking on behalf of the National Center for Health Research. I received my PhD from Johns Hopkins School of Medicine. Our center scrutinizes medical data and provides objective health information to patients and providers. We
do not accept funding from pharmaceutical companies, and I have no conflicts of interest.

    We agree that FDA should get safe and effective new treatments to patients as quickly as possible, especially for devastating disease such as Duchenne. We were hoping for persuasive data on eteplirsen, but with only 12 patients, inadequate control groups, and variation in disease progression, approval would only be appropriate if there is very clear benefit. Sarepta was warned about this in advance.

    Unfortunately, the data do not meet a scientific standard of evidence of effectiveness. While there was an increase in dystrophin, the Western blot shows a total amount of protein below what is estimated to be clinically significant, and a 6-minute walk test was fraught with problems. After less than half a year, Sarepta eliminated placebo controls for a drug intended for lifelong use. It became an open-label study, which could influence the walk test results.

    There are problems with the historical
controls used such as evidence that boys in the control group had little incentive to comply with the walk test, and so some were mislabeled as non-ambulatory. Two of the patients did very poorly on the drug. Sarepta assumes that their early loss of ambulation was related to treatment, but this hasn't been proven. Any one of these problems undermines the study results, but to have all these problems and others is simply unacceptable.

U.S. law requires evidence of safety and effectiveness. The burden of proof lies with Sarepta. If this drug actually works, then Sarepta has failed itself, the patient, and their families by not conducting a better study that could provide convincing evidence showing it works.

Since 2014, Sarepta has been enrolling patients into a larger study, more than 100 boys, but none of those results were provided to the FDA for this meeting. Why not? Even 40 more patients would provide better evidence and the results show clear benefits.
Sarepta should have provided the additional data to FDA to examine and provide to this advisory committee. That's how the process works. This committee should not make a decision based on evidence that has not been vetted by the FDA.

You're hearing from many patients and family members today who believe in this drug. Your role on the advisory committee is to pressure the company to provide scientific evidence before approval, not to pressure the FDA to ignore the lack of scientific evidence.

Your decision today will send a message about whether scientific standards should matter to the FDA. I am very sorry to say that approval of eteplirsen based on today's data would set a dangerously low bar for drugs in the future.

We all want an effective drug for Duchenne. I strongly urge the FDA and Sarepta to work together as quickly as possible to prove whether or not eteplirsen is that drug.

Treatments for rare diseases can be proven on small samples but not based on 12 patients in a
poorly designed study with ambiguous results.

Thanks.

DR. ALEXANDER: Thank you. Will speaker
number 11 please come to the podium and introduce
yourself? Please state your name and any
organization you are representing for the record.

DR. LOWES: I would like to disclose that my
trip was paid for by the Make Duchenne History
consortium, and I am involved in the ongoing
Sarepta trials. My name is Linda Lowes, and I am
the lead therapist on the eteplirsen trial, which
means that along with Lindsay Alfano, I collected
all of the trial outcome measures.

I have been a physical therapist for over
20 years, and I am also a PhD trained researcher.
I would like to speak to concerns about the
administration of the functional outcome measures.

The briefing document questioned whether the
administration of the outcome measures were
identical in this trial and the historical control
group. As a researcher, I understand the issues
surrounding functional outcome measure performance.
To raise the stability and quality of clinical trial outcome measures, a group of international experts formed the Adam [ph] training group several years ago. As a member of this group, I have trained evaluators for almost every clinical trial in DMD, including GSK, PTC, Eli-Lilly for DMD, Biomarin, FibroGen, and others.

By establishing inter-rater reliability, our training group can ensure consistent training. We go to individual sites to establish reliability with the evaluators and perform quality reviews on video assessments from trials and perform quality reviews on blinded trial data.

The lead author on the publication from the Italian natural history study, Elena Mazzone, is a member of our training team. This means that Elena and I present identical trainings on how to conduct functional outcome measures, including when to stop administering the test. We have trained evaluators worldwide, including in Italy and Belgium, as well as at the CINRG sites.

I can assure the committee that consistent
instructions and encouragement designed to achieve maximum effort are given on every test, regardless if the boy is a clinic patient, in a natural history study, or part of a clinical trial.

One of the voting questions is whether decisions to administer the 6-minute walk versus conclusions that the patient could no longer walk were sufficiently objective to allow for a valid comparison. I would like to also alleviate this concern.

In the 2011 Italian Natural History publication, the definition given for two boys who were non-ambulant was that they lost the ability to complete the 6-minute walk test but were still able to take a few steps. Able to take more than a few steps is extremely permissive cutoff for being considered ambulant.

In comparison, you have been watching the boys on eteplirsen walk up to the podium. Differences of opinion is one explanation of why boys continue to perform assessments longer than the other boys. Superior ability is another. I
can personally attest to the quality of my data that you saw presented, and I encourage you to approve the use of eteplirsen.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 12 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WAGNER: Good afternoon. My name is Dr. Kathryn Wagner, and I have no financial interest in the outcome of these proceedings. I am a neurologist at the Johns Hopkins School of Medicine and director of the Center for Genetic Muscle Disorders at Kennedy Krieger in Baltimore, Maryland.

I have cared for boys and young men with Duchenne for over 15 years. I have 2 patients who participated in the 201/202 study, 4 subjects in the current 301 study, and 3 subjects in the current advanced stage 204 study. None of these 9 boys has experienced any drug-related side effects. They are all doing extremely well with
their disease.

I cannot say that eteplirsen has definitely benefited every boy, but it has benefited most boys. Duchenne is a profoundly disabling and fatal condition without exception. After the age of 13, there's a progressive downward decline.

Individual measurements such as the 6-minute walk test may have small day-to-day variabilities, but the course of the disease is consistently downward in the teenage years. Clinically, we rarely see a teenager remain stable over 6 months, and never over 2 years.

Yet to highlight just one subject in the 201 trial, 006, his 6-minute walk test has remained stable over 4 years with values of 355, 329, 359, 332 meters. He is now over 14 years old and still able to rise from the floor. He had no dystrophin at baseline and now has 20 percent dystrophin positive fibers, and 2.47 percent of normal levels by Western blot.

If I were this patient's physician, I would see the stabilization of function over years and
want the option to prescribe eteplirsen.

Muscular dystrophy physicians routinely monitor timed function tests and weigh the risks and benefits of drugs for our patients. We prescribe corticosteroids and follow the rise from floor, run time and/or walk distance, while monitoring the multiple side effects to behavior, bone, and weight, among others. We discuss our findings with the family with whom we make informed decisions whether to continue, reduce, or withdraw a drug.

With corticosteroids, we see much less stabilization of function and much more side effects than what has been demonstrated with eteplirsen. From experience with corticosteroid management, the physicians, families, and communities are well-equipped to make individual assessments of benefit of eteplirsen. As a physician, I want the option to prescribe eteplirsen. We cannot withhold a safe drug from even one boy who may benefit.

(Applause.)
DR. ALEXANDER: Thank you. Will speaker 13 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. NICHOLS: I'm Jodi Nichols.

MS. DUMM: Jen Dumm.

MS. NICHOLS: Make Duchenne History Coalition arranged our travel. We represent our boys and all families participating in the limited ambulation safety study of eteplirsen. My son, Andrew, is 10 years old. He has been on eteplirsen for one year. I remember watching Andrew begin to walk as a toddler. It was so exciting.

Then it was like watching all over again in reverse. As he grew older, Andrew started holding on to furniture, and we had to stabilize and assist him with walking until one day we knew and he knew that he was done walking for good.

I find FDA's assertion that kids who are motivated can walk longer than kids who are not of the highest insult. No one was more motivated than my son to keep walking.
(Applause.)

MS. NICHOLS: But he didn't have the muscles left or the dystrophin available to continue to do so. Then, on April 2nd of last year, Andrew began getting infusions of eteplirsen as part of the limited ambulation study recommended by the FDA in 2014. This has given him back capabilities that we thought were gone forever.

In Andrew's words, "Today at school, I carried my tray by myself. My arms are stronger. I can wrestle with my brother. I can lift my legs now, and I can almost kick." Today, Andrew crawls. He climbs out of bed into his wheelchair. He sits up independently. Posture and fine motor skills are improved immensely. Andrew has experienced zero negative side effects on eteplirsen.

MS. DUMM: My son, 12-year-old John Owen Dumm, shares the same exact story as Andrew. Both Andrew and Owen stopped walking one decade earlier than what is suggested in the FDA briefing documents. Once his infusions started in April 2015, new found strength in every muscle is also
our new norm. Many in our community can attest to the strength he now exhibits that we all thought was gone forever. You have heard from many of them in our written testimonies.

Like Andrew, Owen has experienced zero negative side effects, zero. Before, Owen had difficulty moving his arms. Today, he can feed himself without the use of his mechanical arm. He can write and draw for hours without assistance. He can even hold his own cards when we play card games on game night and move his own pawns in the game Sorry, all because his upper body strength has returned, and not merely because he put his mind to it.

While these small improvements might seem like not much to you, but the return of strength is a massive quality of life improvement. We stand before you not just as two fierce mothers. We stand before you representing a patient community that expects you to do your job.

We expect you to recognize the safety and effectiveness of this drug. We expect you and the
FDA to use the authority and flexibility in FDASIA to approve eteplirsen because it is [mic off].

(Applause.)

DR. ALEXANDER: Thank you. Will speaker 14 please step to the microphone and introduce yourself? Please state your name and any organization you are representing for the record.

DR. HEYDEMANN: My name is Peter Heydemann. I am a pediatric neurologist at Rush Medical Center in Chicago. I have been caring for kids in a muscular dystrophy clinic since the early 1980s. Along with our nurses, I have been administering eteplirsen to patient 004 per a university contract with Sarepta. I've also been paid as a Sarepta advisor at times. The Make Duchenne History consortium funded my travel and hotel here.

With my few minutes, I want to convey two main points. I have observed unexpected stability in the one boy who I care for, who mirrors the accumulated data of the eteplirsen boys. Secondly, there were no significant side effects.
I first observed 004 at age 10 in September 2012 after about 9 months of treatment at Nationwide Children's. He was a spirited boy with mild to moderate waddling and a toe walk gait. Based on his style of movement, I thought he would move slower than he did. He took steroids per study requirements, thyroid hormone for hypothyroidism, and last year transiently, he was treated with growth hormone for about 9 months.

My expectation initially was that his walking would substantially worsen in the upcoming year and certainly over the next 2 years. What I found was that he continued to move around at about the same speed with little change in his style of walking over those 2 years.

It is only in the past year, his fourth year on eteplirsen, that his walking has substantially weakened, especially in the past several months. These degenerative changes are coming much later than I expected.

As a side note, I'd like to point out that 004 is the only boy I've ever cared for who scored
a basket in a school basket game. My functional observations over time were surprisingly favorable compared to my expectations of untreated similar boys, and my observations seemed to correspond well to European natural history group.

In terms of adverse events, 004 experienced none, though we had mild laboratory or family observed side effects, which didn't affect him in the least. The weekly medication infusions were made much easier in his case with the use of a permanent intravenous access port, and then with home infusions.

In sum, my experience and observations tell me that 004's progressive course of weakness was substantially slowed by eteplirsen without any serious adverse events. I believe that eteplirsen if started in younger DMD boys, with more savable muscle, would improve the course of disease even more.

Furthermore, from listening to today's discussion, I believe that eteplirsen meets criteria being reasonably likely to predict
clinical benefit, that it's highly unlikely to
produce clinical harm, and that dystrophin is
produced, and that the many valid criticisms are
not negating of any of this but are reasons for
further data collection after granting accelerated
approval.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker number 15 please introduce yourself?
Please state your name and any organization you are
representing for the record.

DR. CONNOLLY: I am Ann Connolly. I'm a
neurologist at Washington University in St. Louis,
and I have worked with children and adults with
neuromuscular disorders for 27 years. I have been
a consultant for Sarepta but stand to gain nothing
financially from approval.

Please consider what I have to say from the
perspective of a clinical researcher in Duchenne
dystrophy, a neuromuscular pathologist, and finally
with their permission, I speak for Justin and Cole,
who I have followed for 3 and a half years in the
extension study.

I know well the difference between Duchenne and Becker muscular dystrophy as I have cared for more than 150 boys and men with these disorders. If I have a question whether a boy has Duchenne or Becker, I do in fact assess the number of dystrophin positive fibers.

In the recent FDA briefing, it was stated that the percent of positive fibers is not a reliable way to quantify dystrophin. Not only do I disagree with you, I ask you to review those biopsies carefully and note that the fibers with dystrophin are larger and more frequent than any biopsy I've ever seen with revertant fibers.

I believe these dystrophin fibers are driving the clinical effect. Furthermore, because Justin and Cole are so much stronger than I would have expected, if I met them for the first time today, I would have suggested they have muscle biopsies. When I consider their post eteplirsen biopsies and their physical examinations, I would have reclassified them as having Becker muscular dystrophy.
dystrophy. Thus, I do believe that dystrophin positive fibers are a clear biomarker for strength and rescue of muscle.

Now, a minute on behalf of Justin and Cole. I have followed Justin since the age of 3 and treated with intermittent twice weekly steroids. However, at the age of 11 when he entered the study, he had difficulty getting off the ground, and I timed him at 26 seconds, and he subsequently lost the ability to get off the ground.

Based on all natural history that you and I have reviewed, he should have stopped walking by age 13. At age 16 and a half, after recovery from a femur fracture, he is still walking.

My second patient, Cole, was 10 years old when he started the trial and has also done well, despite a fracture at age 11 and a half requiring a cast and no weight bearing for 8 weeks. He has regained the ability to walk and continues to do so at 14 and three-quarters years.

They are both exceptionally bright. These two teenage boys do not require someone to feed
them, take notes, or take them to the bathroom. While I am a strong advocate of corticosteroids, make no mistake about this fact, corticosteroids, whatever the regimen, do not explain the data here. Be careful of a type 2 error. Thank you.

(Applause.)

DR. ALEXANDER: Thank you. Will speaker 15 please introduce yourself? Please state your name and any organization you are representing for the record.

AUSTIN LECLAIRE: Hi. My name is Austin Leclaire. I'm 17 years old. My brother Max has been on eteplirsen for almost five years, and like many in this room, I know what it feels like to watch the drug work and wait for it. After years of waiting, 18 months ago, I was screening for participation in the safety trial.

UNIDENTIFIED FEMALE SPEAKER: All right, the video needs to start over please. It wasn't supposed to be played. Can you start the video over please?

AUSTIN LECLAIRE: I want you to know that I
knew if I didn't perform well, I may not get into the trial, so what you are seeing is my very best effort in the screening, stacking 4 cans, then stacking the fifth can at 48 weeks, and finally lifting my arm over my head at 62 weeks. What does this mean? This means I can now feed myself easier, reach my own urinal, and also transfer myself. This means independence.

My brother and I are Duchenne experts. We've lived with it every day. Before Max started eteplirsen, he was on a sharp decline, and I knew he would be soon in a wheelchair because I remember going through that time when I was 9.

Brothers may not progress in exactly the same way, but I do know that once you start to decline, you keep declining, it doesn't stop. Max was declining. We were about to get him a wheelchair, and then he stopped. The DMD progress -- it's not normal DMD progress, and I know it because I live through it.

I've been on drug 18 months. Normally, boys decline over that time, and I'm not only not
getting worse, I'm getting better. I also know
that we are making dystrophin.

I feel bad that my brother had to go through
4 biopsies to prove this over and over again and
that data needs to be used now to review the drug.
I hear you say that 0.9 percent is disappointing.
In order to use a word like that to describe making
dystrophin in a disease like Duchenne, I can only
guess that you don't know anything about Duchenne.

Making 0.9 --

(Applause.)

DR. ALEXANDER: Please hold your applause.

AUSTIN LECLAIRE: Making 0.9 percent is
amazing. It lets me feed myself. It keeps Max
walking. It gives us a chance. 0.9 percent is not
perfect, but it is life changing. My friend, Jake,
needs the next drug, exon 45. He has just had to
have a painful spinal surgery that I would like not
to have to go through because I am on eteplirsen,
and my back is much stronger because of it.

It's time to listen to the real experts. So
to make that easier for you, we brought them all
here today. Please use them.

(Laughter.)

(Applause.)

DR. ALEXANDER: Thank you very much. Once again, please hold your applause until the last speaker has spoken. Thank you very much.

Will speaker number 17 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. GULATI: My name is Neera Gulati, and I'm representing Suneel's Light. I'm presenting my perspective as a physician. The people best able to assess the efficacy of this drug are the experts who have cared for Duchenne patients. Thirty-six doctors who have cared for over 5,000 patients for 15 years have presented their support.

The FDA is accustomed to evaluating drugs for common highly prevalent diseases such as hypertension and diabetes. Statistically, it is easier to collect data in such diseases. With Duchenne, due to the rarity, heterogeneity, and the shortened lifespan, this is not possible.
Statistics are not an adequate tool to assess ultra-rare diseases. Consequently, Congress passed in 2012 FDASIA, a bill I and others in this room supported. In the FDA briefing documents, it was very disappointing for me to read the FDA declared support for FDASIA and yet still insist on data that cannot be collected for a rare disease.

Well-controlled studies as interpreted by the FDA are not easily achieved if at all in orphan disease populations. This is not honoring the spirit of FDASIA. Following FDASIA should not be optional.

The FDA feels they can better assess disease trajectory based on data they select, and they have discounted specialists' clinical experience rather than valuing the information provided. If I as a family physician inform my patient there is a new drug specialists are recommending for his rare, terminal, life limiting disease that has no significant side effects, but I am not going to give him access to this drug because my interpretation of the data conflicts with the
specialist's, I am certain he would leave my
practice and seek expert opinion elsewhere,
probably from one of those 36 doctors.

I have had the privilege to live in Buffalo,
New York next to Roswell Park Cancer Institute and
witness the prognosis for cancer change from a
death sentence to a treatable disease. I watch my
patients try treatments with serious side effects
that definitely had mortality risks and uncertain
benefits. They wanted these options. Why not for
Duchenne?

In the 1950s, childhood leukemia had
100 percent mortality rate. Clinicians such as
James Holland from Roswell Park and [indiscernible]
Frei from the NCI were convinced medical orthodoxy
had it backwards in regards to treating childhood
leukemia. They spearheaded novel combination
treatments with serious side effects. This was
unheard of in the late '50s. Today, combination
drug treatments for cancer is standard, and
childhood leukemia has a 90 percent cure rate. Why
not for Duchenne?
It is clear to me the FDA will never feel comfortable with ultra-rare diseases. It is also clear to me from the experts that exon skipping drugs meet the criteria for FDASIA and are worthy of accelerated approval.

I am hoping the advisory committee members will have the insight and judgment to realize that eteplirsen should be granted accelerated approval. I'm hoping that FDASIA will be respected and enforced.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 18 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. ARNOLD: Good afternoon. My name is Louise Crow-Arnold, and the Make Duchenne History Coalition paid for my travel today. The diagnosis of Duchenne to a family is devastating. To know that your child, who has just begun to discover things, will gradually have each development taken away is particularly cruel.
With no treatments available in the UK, and with the knowledge that if we were to do nothing, his early death would be inevitable, we sought out the most promising, effective, and safest drug that could treat our son, Leon. We moved our family to the United States to take part in the eteplirsen trial.

As parents, we had enough faith in the data that was made public to move across the world so that Leon could be in a clinical trial. This huge upheaval has meant we have left our jobs, home, our son's schools, family, and friends behind.

Since taking eteplirsen, Leon has shown increasing signs of strength. He performs the Gowers Maneuver far less when rising, and his falls are less frequent. He enjoys drawing and writing far more as he tires less with these activities, and his hand grip has strengthened.

His stamina has increased, and he can cover greater distance before fatigue sets in. His stroller is staying in the garage far more than when we arrived in America eight months ago. Our
biggest reward is that Leon can hug us tighter.

   At no point have we experienced any side
effect with eteplirsen, either during the infusion,
afterwards, or at any time during the week between
doses. When Leon was born, we stared at our
sleeping child in wonder, and it is then as a
parent that you vow you will always love them and
do anything you can for them.

   That is why we have moved halfway around the
world. That is why we are here today, for Leon,
and for every other child who has the misfortune to
be born with Duchenne.

   This drug is not a false promise. We have
witnessed the efficacy of this drug. We are not
just desperate parents, as often described in the
media. We have listened to our doctors. Standards
of efficacy matter, but flexibility matters too.

   Eteplirsen patients are experiencing delayed
loss of motor milestones. The data is sufficient
to approve eteplirsen, and the FDA has the
authority to grant approval. Thank you.

   (Applause.)
DR. ALEXANDER: Thank you very much. Will speaker 19 introduce yourself? Please state your name and any organization you are representing for the record.

MS. EICHELBERGER: My name is Kim Eichelberger, and my son Cole has Duchenne. Our travel was paid for by the Make Duchenne History Coalition. In August 2011, when Cole was 10 years old, he was selected as one of 12 participants in the eteplirsen 201 trial. He was selected because he appeared to be on the cusp of decline.

He walked with lordosis to compensate for quadriceps weakness. He had a wide stance because he needed the support, and he had the typical Duchenne waddle when he walked. In short, he did not look like a child who would be walking for years to come.

We now know that for the first 24 weeks he received placebo. During this time, he declined significantly in his 6-minute walk, then he started eteplirsen. The FDA's briefing documents argue that boys on eteplirsen are progressing exactly as
one would expect given the natural history of the disease. They argue that several of the boys have reached distances on the 6-minute walk that would suggest they will come off their feet shortly, signaling the drug doesn't work.

My son is one of those referenced boys. At the 3-year mark, my son walked right around 100 meters on the 6-minute walk test. Six months later, at the 3 and a half year mark, he walked only 50 meters on the 6-minute walk test. Any clinician will tell you based on that trajectory that his walking days were numbered. And then 6 months later, at the 4-year mark, my son still walked 50 meters on the 6-minute walk test. And then just a few weeks ago, at the 4 1/2 year mark, my son not only completed the 6-minute walk test once again, but after the visit, he informed us he had walked further than he had on the previous two visits, walking further than he had on the test in over a year.

I'll say that again because it needs to be heard. At 14 and a half years old, instead of
coming off his feet like the briefing documents
predicted would happen, my son improved his
distance on the 6-minute walk. His is not the
story of a Duchenne outlier who continues to
perform better than one would expect. His is the
story of a Duchenne patient who was falling off the
class toward irreversible decline and was somehow
yanked back onto the ledge.

I should also mention, because it is in the
briefing documents, that Cole has never had an
intensive physical therapy regimen. In fact, over
the last 4 and a half years, he has received
physical therapy for a total of about 6 months. In
addition, his steroid dose has remained at roughly
half of the weight recommended dose of
0.9 milligrams per kilogram.

Cole will enter high school this year still
on his feet, which is something my husband and I
could not have imagined possible when we were given
his diagnosis. I can say with confidence that the
life my family is living would be very different
than it is today were it not for eteplirsen.
I believe if you were to ask his doctors, Drs. Ann Connolly and Jerry Mendell, both of whom are here today, that they would agree. In fact you've just heard Dr. Connolly's opinion on Cole's progression.

This drug should be granted accelerated approval so that anyone who can be helped by it has access and can benefit the way Cole has while we wait for definitive answers from the confirmatory trials. Thank you for the opportunity to speak today.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 20 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. ELLSWORTH: My name is Terri Ellsworth from Pittsburgh, Pennsylvania, and my son Billy, age 15, has been receiving eteplirsen since August 2011, receiving 30 mgs/kg of the drug. The Make Duchenne History Coalition arranged for our travel. Instead of spending the most important
3 minutes of my life talking about Billy's accomplishments and success on eteplirsen, I have to spend it talking about the misleading briefing documents that were released by FDA's neurology division.

In these documents, FDA states that boys on eteplirsen, quote, "Appear to receive optimal care, including intensive physical therapy and intensive steroid regimens," close quote, claiming that PT and steroids are responsible for these boys' stability rather than the eteplirsen.

We want the panel to know that the Columbus trial family strongly disagree with these comments. Our boys either received minimal, standard, or no PT throughout the trial. In addition, most of the boys on eteplirsen are massively underdosed with steroids.

My son spent the entire trial at 21 milligrams of deflazacort, which is nearly half the recommended dose. The advisory committee process is supposed to be an unbiased panel, but with the FDA's briefing package, the committee has
been tainted and led astray with misrepresentation in the information that they received.

I read posts daily on social media from fellow Duchenne parents about their daily caregiving and challenges that their boys face. I read it, I understand it, I get a lump in my throat, but that is not my life. I don't wake several times a night to turn my son in bed, he turns himself.

I don't have to feed my son, he feeds himself, and then carries his dishes and glass to the sink. I don't have to brush my son's teeth, he does it himself. I don't dress my son, he dresses himself, and then comes down the stairs for breakfast. I don't bathe my son, he does it himself.

Billy was not and is not an outlier. Before eteplirsen, Billy was an extreme toe walker. He consistently walked with his heels 3 inches off the ground, which typically indicates the end of ambulation is near. Now, almost 5 years later, he is still walking, and his heels are much closer to
the ground. This is not placebo effect, this is eteplirsen still at work.

MR. ELLSWORTH: My name is Billy, and I have been receiving the eteplirsen drug since I was 10 years old. You should approve eteplirsen because I am very strong and still walk a lot. I'm afraid that if you don't approve this drug, I will become very weak and not be as independent like I am now. It makes me sad and afraid that I won't be able to do all the things that I can do now.

I see other boys my age and younger that cannot do what I can do, and it makes me mad that they also cannot have the drug. I hardly ever have to ask my parents to help me with anything because I can do most everything in my daily life by myself.

I'm going to beat this bloody disease, but I need your help. So please help me and my friends and do the right thing. FDA, please don't let me die early.

(Applause.)

DR. ALEXANDER: Thank you very much. Once
again, please hold your applause until the final
speaker has spoken.

   Will speaker 21 please introduce yourself?
Please state your name and any organization you are
representing for the record.

   (Applause.)

   MS. MILLER: My name is Debra Miller. I'm
the founder and CEO of CureDuchenne, which has paid
for my travel. CureDuchenne provided funding to
Sarepta in 2010 to conduct studies that enabled it
to get off clinical hold and move into human
clinical trials for eteplirsen.

   Duchenne, unlike other neuromuscular
diseases such as MS, has no ebbs and flows or
remissions, only a downward trajectory of loss
first of ambulation, then autonomy, and ultimately
life. Our kids have been taking steroids, which
carry multiple side effects and have uneven
benefits. Fortunately, we've been able to use
off-label steroids or buy them from other
countries, otherwise our children wouldn't not have
been able to benefit from them.
Exon skipping works. It may not be the complete cure, but it helps many boys extend ambulation and improve their quality of life. We cannot buy it off-label or order it from another country. Your approval is our only hope for access. The current exon skipping trials were designed many years ago with limited knowledge of Duchenne’s natural history.

You, the FDA, can insist on a perfectly designed trial and sacrifice this current generation of Duchenne boys, or you can allow access to these drugs while we perfect clinical trial designs for the future.

CureDuchenne has sponsored cTAP, the first collaboration between biotech and pharma companies created to apply statistical analysis to understand the natural progression of Duchenne and design more informed clinical trials.

We encourage the FDA and sponsor companies to take advantage to cTAP and meanwhile use the accelerated approval program to allow the use of eteplirsen. Use your power to remove the drug if
it is demonstrated to be unsafe or ineffective post-marketing.

To cure Duchenne, we will need a combination of therapies to treat the whole disease. Exon skipping is a cornerstone of this approach. CureDuchenne is funding the development of multiple drugs, but we cannot test drug combinations until the first drugs are approved.

I have a son with Duchenne. His name is Hawkin. He is 19 years old and just finishing his freshman year at USC. He's a news editor for the Daily Trojan. He lives independently without an aide. Although he uses a scooter or power chair for distance, he is able to walk and take care of himself and drive his friends around town.

He has approximately 3 percent of normal dystrophin. Even small amounts of dystrophin can add years of independence and improve quality of life, but we need to start treatment when they are young to realize the true benefit.

I respect the FDA's caution in setting a precedent in approving new drugs, but our kids are
not a precedent, they are real live human beings and they are short on time.

An FDA official once told me, "The worst thing we can do is approve a drug and then have to pull it off the market." I argue that the worst thing you can do is deny access to a drug and then find out it works too late, after we have lost a generation of boys. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 22 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. McSHERRY: Hi. My name is Jordan McSherry. Today, I'm introducing my brother, 20-year-old brother, Jett McSherry's video testimony. This video was filmed in his college dorm room. So feel free to laugh. Audio.

(Video played and transcribed.)

MS. McSHERRY: [Indiscernible] I feel pretty -- I've noticed a few changes since [indiscernible]. I started to take eteplirsen in
October of 2014. Right now, it's April 2015, and I've been on it for around about 20 weeks now.

I feel pretty -- I've noticed a few changes since I've -- since I've been on this drug. I've noticed that I have more strength than I usually have. I can do more stuff on my own. I can eat by myself a lot easier.

I sleep a lot better at night. I don't snore as much anymore. I don't get tired as easily. I don't feel so tired at the end of the day [ph] than I did before. I can also open cans myself, which I couldn't do before pretty easily.

AIDE: I've been working with Jett since the beginning of the school year, and one thing that I've noticed [indiscernible] better since he's been on the drug was at first his snoring was really bad, right, could barely fall asleep at first and then after [indiscernible] once he got on the drug, I'd have to say right around probably December, winter break, around that area, he just got a lot better and it's -- I mean every one snores but it's not nearly as bad as it's ever been and it seems to
be improving every day.

Another thing with him sleeping is he likes to put his leg up when he sleeps but that's something that he asks me to do for him. And then one time I woke up in the middle of the night and he had his leg up himself and he did it himself without anyone asking.

Just little things like he used to ask me to get him food, and when he needed food I'd either have to help feed him or open the bag like chips but now he can open a bag of chips by himself. Another example is this water bottle, I used to have to feed him the water bottle, but now he can for the most part grab it himself and put it up to his mouth, but also I can leave it on the desk and he can just come over and grab it by himself.

(Laughter.)

AIDE: [Indiscernible] And also other things like his laptop, he can -- if I left his laptop on the desk [indiscernible] controller or the video game controller I can just leave it right there and then he -- [mic off].
Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 23 please introduce yourself? Please state your name and any organization you're representing for the record.

MS. SECKLER: My name is Tracy Seckler, and my son Charlie has Duchenne. I'm the cofounder of Charlie's Fund, a public charity that has directed $38 million since 2004 into a varied portfolio of medical research and drug development programs, including exon skipping and other therapeutic approaches.

Here's a fact that is not in dispute today, not in the medical literature, not in the FDA briefing documents, not among the experts, and not in our personal experience. Two clear warning signs let us know that loss of ambulation is coming soon. When a boy loses the ability to independently rise from the floor, he is highly likely to lose ambulation in 1 to 2 years. And scores of 13 and 9 on the North Star Ambulatory Assessment predict loss of ambulation in 2 and
1 years, respectively.

These warning signs let us know when we can expect the next loss milestone. Amy, Scott, Lisa, Valerie, and I watch anxiously and fearfully each and every day for those signs, and there is nothing we can do to stop it or slow it down because our children are not on eteplirsen.

The boys on eteplirsen who got these warning signs have experienced something different. Based on what we all agree upon about the sequential loss of milestones, many of the eteplirsen boys should be in wheelchairs by now, but they are not.

FDA suggests that perhaps these boys are outliers, that all 10 of them would, without treatment intervention, progress relatively late, but the boys selected for the eteplirsen study 5 years ago were not the strong ones, the late progressers. The stories you have heard from them and their physicians today, including toe walking, lordosis, and frequent falls prior to starting treatment, support and fit with the data collected in the clinical trial setting.
One boy lost the ability to rise from the floor 3 years ago, yet today he can still walk. Another lost the ability to rise from the floor 2 years ago; today, he can still walk. A third boy lost the ability to rise from the floor a year and a half ago; today, he's still walking.

A look at the North Star scores provides more evidence that these boys should have lost ambulation by now. The three kids who dropped below a score of 13 more than 2 years ago are still on their feet, and the 4 who dropped below a score of 9 more than a year ago, still walking.

These boys are deviating significantly from their natural history counterparts who were rigorously selected to provide the closest possible match. Importantly, they are also defined their own predicted natural history based on uncontested signals of rate of disease progression.

Later today, you will be asked to consider several questions. Theoretical concerns about the limitations of natural history notwithstanding, this data provides the information you need to
answer questions 5 and 6. As for question number
7, these boys are the answer. These boys are the
substantial evidence of eteplirsen's treatment
effect. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker number 24 please introduce yourself?
Please state your name and any organization you're
representing for the record.

MS. McNARY: My name is Jenn McNary. My
travels were supported by the Make Duchenne History
Coalition, and this is Max. I am told that I was
the first person that knew the drug now called
eteplirsen worked, before any of the data was
released.

It's not because I'm a scientist or a
clinician, it's because one of my sons, Max, was
one of the first boys in the U.S. to receive the
drug. His older brother, Austin, who you've heard
from, had already stopped walking at 10 and a half
years old. He was unable to get into the trial
because he was unable to walk, forcing me into a
situation where there was essentially an open placebo-controlled trial in my own home.

At trial start, Max was 9 and a half and on a downward spiral. It was Austin who told me at the time, "Max is falling a lot, Mom. I think he needs a power wheelchair." We ordered one. The FDA states in their briefing document that there's a wide range of loss of ambulation for boys amenable to exon 51 from 8 to 18 years.

Those in this room who know Duchenne know most lose ambulation between 10 and 12 years. So why is the FDA so focused on outliers? Our sons were not chosen for the trial because they are outliers, they were typical boys. The boys in the study were chosen because they were declining, typical for Duchenne, until they began the treatment with eteplirsen. This is when their progression became atypical.

I was skeptical at first because the trial was blinded and placebo-controlled. I didn't even know if Max was on drug, until the day that I knew. Max opened a milk container at the airport for the
first time. His grip has always been weak. He always handed the jug to me to open, but that day he opened it. Small changes turned to bigger changes over time.

Max was choosing to ride in his wheelchair less and less until he decided not to use it at all. He was not coming home from school tired, despite abandoning the chair. It had been with him daily since kindergarten. He started participating normally in gym class. And most importantly, he totally stopped collapsing. We cancelled that order for a power chair, and 4 and a half years later, we haven't seen the need.

Max is still declining some. Over 4 years, his walk test has remained about the same, which in itself is amazing to have this kid just dangling on the edge of a cliff and stay there for 4 years without falling off.

But more importantly, Max's daily life and level of independence has changed. Last week, 14 and a half-year-old Max got out of his bed. He got dressed. He put on his shoes and his backpack
and he walked out to the school bus unassisted.

I am incredibly proud to be standing here saying the same thing I’ve been saying daily since day 1, eteplirsen works. Only today, I’m happy to be surrounded and supported by sound dystrophin and clinical data, physician, researcher, and patient testimonies similar to my own.

I want to impress upon the panel that a recommendation for approval is the only acceptable outcome of today’s meeting. And if you ask me, it's incredibly overdue at this point. We are the lucky ones, the boys in orange. So many are still waiting. Let's do the right thing.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 25 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. PARTRIDGE: Yes, I'm Terry Partridge, and I'm currently professor of systematic integrative biology at George Washington medical school here in DC. Before that, I was in London
where for about the past 45 years, I've worked on research on muscular dystrophy, and I was head of the Medical Research Council Clinical Sciences Centre muscle group.

My main area of interest is the mechanisms of muscle repair and of exon skipping, and I think the two are beginning to become involved with one another. One of the problems that came up today, regularly, was the inconsistency about dystrophin measurement between different studies, and across time, and within the same manual, and between muscles. And I think there's a perfectly good explanation to this, which I think should be taken into account when considering the data.

On the screen at the moment is an old slide from Francesco Muntoni's original systematic trial showing perfectly good post-dystrophin, pre-post-dystrophin differences there. One of those is slightly more overloaded than the other, but it's good data. And it shows that there is dystrophin there. And the question is, what does it do?

So the problem with the exon skipping is
that it works on very small groups of muscle cells. When you look at these biopsies, and I was hoping to put one up, you find tiny groups of muscles, muscle fibers that are affected. These are about a millimeter cubed in size. And if you were to try to find those with the 10 or 20 micrograms of a muscle biopsy, you might find two or three of those in one of your biopsies, in which case you'd find dystrophin, or you might miss all of them, in which case you wouldn't find any dystrophin. And I think this accounts for quite a lot of the lack of consistency.

I see I'm running out because my slides are not working. So the other thing I would say is that you need to have something more easily evaluable than the amount of dystrophin that's present. You need to use biomarkers that are beginning to come up that are much less invasive, like urinary proteins that are lost from muscle during the stages of degeneration and regeneration. And you can show quite easily, as I would be doing if the slides were working, that there is a -- it's
too late -- that there is a distinctive benefit.

Can I go back to that slide or not? Yes.

The last one, that's it. I've lost it. I don't know. [Off mic.]

DR. ALEXANDER: I'm sorry. Can you extend -- can you turn on the microphone, please, so the gentleman can have just a second or two more for his comments?

(Applause.)

DR. PARTRIDGE: So these two slides up there show basically following two proteins in the urine that are lost from muscle fibers when they're damaged, and it shows the effects of a morpholino treatment in the mouse to skip the exons and restore dystrophin. And it shows that -- can you go on to the last one again?

Yes, that's the one. It shows that with the treatment, the lower of those curves, in both sides, the treatment takes down those biomarkers in the urine. These are easily accessible biomarkers. They're the same biomarkers as are being used in Duchenne boys, and they would, I'm sure, form the
basis of any trial should the committee agree to an accelerated approval for the continuation of eteplirsen.

DR. ALEXANDER: Thank you very much.

(Applause.)

Will speaker 26 please introduce yourself? Please state your name and any organization you are representing for the record.

MR. BOWER: Hello. My name is Caden, and I'm one of the 12 boys in Sarepta's eteplirsen --

DR. ALEXANDER: Can you speak into the microphone a little bit more, please?

MR. BOWER: I ask that you please approve this medicine. If it is not approved, I am scared that I will lose the ability to walk, and I don't want this to happen to me. This medicine is keeping me walking and allowing me to keep up my day-to-day activities and remaining stable. Thank you.

MS. PEREZ: Hello. My name is Beth Perez, and the Make Duchenne History Coalition paid for our travel. And my 12-year-old son is one of the
12 boys in Sarepta's study. You heard it from him, it is keeping him walking, and he is here standing next to me today.

Caden has faithfully devoted nearly five years of his life to this exon skipping drug. He has not been on placebo and has been receiving 50 milligrams of the drug throughout the study.

Eteplirsen is giving my son a fighting chance. I would have expected him to have more of a physical decline by this stage of his life, and I feel that he would be completely non-ambulatory if it weren't for this life-saving drug. It is safe and effective with zero side effects.

One thing I can tell you is that through receiving these eteplirsen treatments, he is able to live a more functional life than that of a 12-year-old DMD patient not receiving the drug. For example, a typical DMD boy cannot pedal a bicycle, but Caden is remarkably able to pedal a few feet on a therapeutic tricycle and has less falls since receiving the drug.

Caden is receiving below the recommended
dose of steroids. Until October 2015, he was on 18 milligrams of deflazacort. At that point, Dr. Mendell increased the dose to 24 milligrams.

Caden does not receive any intensive physical therapy. He receives therapy as advised for any child with DMD. Caden's therapist has seen and said that he has increased endurance for walking activities without the need of assistive devices.

He has participated in aquatic therapy sessions for longer periods without excessive rest breaks, and he has shown drastic improvements in his active range of motion, most notably in his hamstrings and hip flexors.

As parents, it's difficult seeing your child struggle, but to witness them tackle life's seemingly simple daily tasks is a heartbreaking battle that any DMD parent can relate to. I don't know want to tell my son that his dreams for a future are going to be taken away from him.

The boys fighting DMD are the strongest warriors that I know of, and if this drug helps to
make their world a little easier to live, then I
don't see any ethical reason as to why this
medicine should not be approved.

We support Sarepta and eteplirsen one
hundred percent. This drug means a future and a
promise to my son, our family, and every Duchenne
boy. Thank you for your time.

(Applause.)

DR. ALEXANDER: Thank you very much Will
speaker 27 please introduce yourself? Please state
your name and any organization you are representing
for the record.

DR. MICELI: I'm Carrie Miceli, professor of
microbiology, immunology, and molecular genetics
and co-director of the Center for Duchenne Muscular
Dystrophy at UCLA. For the past 10 years, my own
laboratory has been well funded to explore
mechanisms for boosting the activity of morpholino
directed DMD exon skipping in mouse and human
models. I'm familiar with measuring and
interpreting expression of skipped dystrophin
proteins.
One stated concern relates to the fact that the pre-treatment control tissues was exhausted, and thus controls from the PROMOVI pre-treatment biopsies were included in analysis of biopsy 4 challenging interpretation.

It's important to note that two patient pre-treatment samples were included in both assessments of biopsies 1 through 3 and biopsy 4 by immunohistochemistry. These samples should serve as internal controls that allow for the validation of the new set of controls, as typical of the treatment cohort. The findings are interpretable and clearly support induction of dystrophin.

Exon skipping uses morpholino and is known to induce patchy dystrophin expression. Therefore, assessment of eteplirsen induced dystrophin requires consideration of both the absolute amount of dystrophin present as well as its distribution.

Given the level and distribution of induced dystrophin being observed, it's reasonable to expect that some positive fibers express as much as 5 to 12 percent of normal dystrophin, levels
clearly predicted to impart some production of myofiber's contraction induced damage.

Data from studies in BMD and DMD patients and in mouse and canine models support the suggestion that relatively low levels of dystrophin can be functionally significant even if only expressed in a limited number of fibers.

Of note, the number of dystrophin positive fibers is not expected to be equal to the percent of normal dystrophin protein unless each fiber expresses 100 percent of normal levels of dystrophin, which is clearly not the case. There is no inconsistency there.

In response to the first set of briefing documents, 36 prominent scientists and physician experts in Duchenne provided FDA with a letter clarifying issues raised. We ask that the letter be made available unredacted to the advisory committee. If you have not seen it in its entirety, we hope you can gain access today.

Quoting from that letter, "We conclude that there is strong evidence of induced dystrophin
production upon prolonged eteplirsen exposure."

The letter goes on to say, "The findings of this trial are sufficiently robust to support the proposed mechanism of action of eteplirsen to provide a plausible explanation for the relative gain in function observed within the treatment group, and serve to bolster confidence that there's a positive treatment effect."

I am also the mother of Dillon Miceli Nelson who lives with Duchenne. Given the strong safety profile, I'd be keen for Dillon to be on this drug if it were pertinent.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 28 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. KELLY: Hi. My name is Wendy Kelly, and I'm here today with Susan Patterson. The Make Duchenne History Coalition arranged our travel. We're here today to speak about our children's experience on eteplirsen and how our sons have been
performing everyday activities easier since
starting the drug.

My 8-year-old son, Jackson, has been on
eteplirsen since January 2015. Susan's 8-year-old
son, David, has been on eteplirsen since July 2015.
Both of our boys are part of the confirmatory trial
that was clearly guided by the FDA in the April
2014 guidance. In that guidance, FDA also guided
for eteplirsen safety trials on younger Duchenne
patients and those at later stages of the disease.

Since they started on eteplirsen last year,
our boys have stabilized and they have started
doing things that they could not do before,
everyday things that normal 8-year-old boys take
for granted, like opening car doors, getting off
the floor with ease, easily bending over to pick up
things off the floor. We truly believe that
eteplirsen has changed the trajectory of their
disease.

Our children may have a future now that
might give them the opportunity to walk well into
their teens. With that ability comes independence
that most boys living with Duchenne lose very quickly after going into a wheelchair.

Our observations verify and confirm what Sarepta's data on the original 12 patient study show, that treatment of eteplirsen can cause a real and concrete impact on the lives of Duchenne patients.

In addition, it is necessary to note that neither of our boys have experienced a single negative side effect from being on eteplirsen. This drug has our stamp of approval. We believe it is unfair of the FDA to make a comparison to Becker muscular dystrophy. The comparison should be to Duchenne. Eteplirsen is allowing our boys to produce dystrophin.

We would love to turn our sons' Duchenne into Beckers, but that should not be the standard of measurement. Any benefit that allows our boys to walk longer, breathe longer, or just make it through the day is worthwhile.

The only reason our children were able to receive eteplirsen is because the FDA allowed for
confirmatory trials in their 2014 guidance to the company. By the time these confirmatory trials are complete and the data is analyzed, it could be another three years.

The human cost of not approving this drug now and waiting up to three years for confirmatory trials to be complete would be massive. Children will have lost the ability to walk, to pick themselves up off the ground, and to feed themselves.

We all know what the end result of Duchenne is, and the patient testimony here today should tell you all that you need to know, the benefit of eteplirsen far outweighs its risks. From the Pattersons and the Kellys, please approve this drug.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 29 please introduce yourself? Please state your name and any organization you are representing for the record.

MR. LEFFLER: My name is Mitch Leffler. The
Make Duchenne History Coalition arranged my travel here today, and I have a 12-year-old son who has been on drisapersen and is now on eteplirsen.

The decision we're facing today would be an easier one if we had a large placebo-controlled data set, but here's the problem with collecting that data set for exon 51. We're already starting with an orphan disease. Then you remove the 87 percent of patients that aren't amenable to this exon skip.

Out of the remaining 13 percent, you take away the one-third of boys who are too cognitively affected. Then you need to remove the boys who have already participated in an exon-skipping trial and are no longer drug naïve. Then you subtract the families that live too far from a study site to travel once per week. Then we lose the families that have chosen to participate in a less demanding clinical trial.

Then you subtract the families that cannot afford clinical trial participation. For example, my own family has spent over $40,000 in childcare
and lost wages to participate in two clinical trials.

Lastly, you need to subtract the boys that do not fit the inclusion criteria, that are too old or too young, their pulmonary or cardiac function isn't strong enough, or maybe it's something as simple as elevated white blood cell count during the screening. But they may not fit in the narrow 6-minute walk criteria that's necessary to show a treatment effect over a shorter period of time.

The result is that you're left with so few boys that you end up relaxing the enrollment criteria in order to get the numbers. And once that happens, if you're using the 6-minute walk, you've introduced so much variability into your trial that you've changed science into randomization roulette.

Some may say extend the duration of the trial, keep children on placebo for a longer period of time, but this trial includes muscle biopsies under general anesthesia. If you think that procedure is minor, you should know that my son has
a permanent limp from his two muscle biopsies in his quadriceps.

So once you introduce this kind of procedure, absolutely a more minor increase over minimal risk, you have to involve the prospect of direct benefit for every participant, a requirement that is not satisfied by participation in a placebo arm.

So we all know that a large scale, long-term, placebo-controlled trial would give us some of the answers we're looking here today. But here's the deal. We can't have one. It's not numerically possible, and according to FDA's own guidelines on pediatric clinical trials, it is not ethical.

So when we can't have the optimal data we want but we still need to make a decision, what do we do? Do we abandon a promising treatment or do we become more interested in getting at the truth than focusing on methodological concerns?

That is a question we're answering today, and it's a question that's going to be asked more
and more often with genetic targeting of rare
diseases. The world's leading experts are here
today telling us that what they're seeing is
unusual. Our boys are changing in front of our
eyes. It can't be ignored. It can't be explained
away. And it needs to be acknowledged today.
Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 30 please step to the podium and introduce
yourself? Please state your name and any
organization you are representing for the record.

MR. WESLEY: Yes, Mr. Chair, my name is
Keith Wesley. Make Duchenne History Coalition paid
for my lodging. My son, Jake Wesley, is 15 years
old, has Duchenne muscular dystrophy. Jake's not
in any current clinical trial. Jake's lack of
abilities and limitations due to the unfortunate
circumstances are what have brought me before you
today. I have slides but they're not coming up.
Oh, here you go.

DR. ALEXANDER: And I believe you have
control of the slides or no?

MR. WESLEY: Yes, they are up now. Thank you.

DR. ALEXANDER: Very good.

MR. WESLEY: Jake lost the ability to walk at 8 years old. After being confined to a wheelchair for several years, Jake developed severe neuromuscular scoliosis, a condition that occurs in a large majority of the boys with the more severe phenotype, those boys that produce little or no dystrophin.

Jake underwent an extremely invasive 10 and a half hour spinal fusion surgery this past year. I'd like to draw your attention to those photos. Earlier today scoliosis was mentioned. Here it is. And while pictures tell a thousand words, they don't tell you the fear that these boys endure for months in advance of this surgery.

Although Jake is not in the eteplirsen trial, his best friend, Austin Leclaire, is. Jake and our family have known Austin for almost 10 years. Prior to Austin being in a trial, his
motor skills almost mimicked Jake's. Now Austin can lift his hand above his head. And prior to Jake's surgery he contacted a number of boys with DMD who had spinal fusion surgery.

The majority of these boys said their biggest regret was the fact they could no longer feed themselves. It seems like such a small thing to ask, the ability to feed yourself, but to these boys, it means the world.

While Austin has regained the ability to raise his arms above his head and transfer to bed independently, Jake can no longer feed himself. While Austin has regained the ability to toilet independently, Jake completely is dependent on us for all his personal care. After years of progressing identically, there should be no reason that Jake and Austin would start to differ in progression unless the drug works.

I'm an elected official in the state of Pennsylvania, and I ran for office because I wanted to make a difference. I didn't just want to make a difference, I did make a difference. I like to
believe the same of all of you. Why else, if not to make a difference?

In closing, my intent is what Congress wants, and voiced through FDASIA, and that is to deliver safe and effective drugs for the treatment of rare and severely life-threatening diseases. I don't know a better candidate for accelerated approval than a drug that apparently its only side effect is extended life.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 31 please introduce yourself? Please state your name and any organization you are representing for the record.

MR. VAISH: Hi. My name is Ryan, and I have Duchenne. I am 13 years and 10 months old, and I have been on eteplirsen for almost five years without missing a single dose. Ever since I was diagnosed, all the doctors are saying by the time I'm 13, I would be in a wheelchair and not be able to do things I can do now. But since I've been on the medicine, I am still walking, swimming, playing
with my friends and my dog, which people say I could not do at this age.

If someone asks me if the medicine is working, I say I believe it is because I'm doing stuff I should not be able to do at my age. If you are 100 percent sure that this medicine is not working, don't approve it. But if you're not 100 percent sure, then approve this medicine, help other boys who share my struggle. Thank you.

(Applause.)

DR. ALEXANDER: Thank you. Please hold your applause.

MS. VAISH: I am Ana, and Make Duchenne History Coalition arranged for us to be here today. I am Ryan's mother. As he said, he is 13 years and 10 months old, and one of the 12 boys getting eteplirsen since 2011. He hasn't missed a single dose and has had no safety issues.

When Ryan started the study, he was declining. He walked with lordosis and his toes pointed inwards due to the weakness in his hips, both signs that he would lose ambulation soon.
He did not look like a child with Duchenne that you would expect to see walking four years later. However, since 2011, Ryan has maintained the same energy and ability to do day-to-day things, like walk, go to school, play with his friends, go swimming, and shower by himself.

We have not given Ryan any more PT or anything other than the recommended care. Before being on the trial, Ryan used to come home from school very tired. Now on eteplirsen, he comes from school and goes straight into the pool. In fact Ryan has been receiving below the recommended dose of steroids.

Until March of 2015, he was taking 18 milligrams of deflazacort, half of the recommended dose. At that point, Dr. Mendell increased his dose to 24 milligram because it was still very low. That is still below the recommended dose of 33 milligrams according to his weight today.

The 0.9 increase in dystrophin may not mean much to the reviewers at FDA, but come, look at the
10 boys that are still walking. Come live in the 
shoes of these children, of my son Ryan, and it is 
meaningful.

Every day that Ryan maintains his ability to 
walk and live longer matters. Maintaining the 
ability to do day-to-day things matter. More time 
matters. More time for our family and hope for 
even more treatments that will reach your desk soon 
for approval. The first safe and effective 
treatment is on your desk today. Please recommend 
approval of eteplirsen.

(Applause.)

DR. ALEXANDER: Thank you very much. Will 
speaker 32 please come to the microphone? Please 
state your name and any organization you are 
representing for the record.

MS. DWYER WILLIS: My name is Alison Dwyer 
Willis. I am the mother of Jack and Nolan Willis, 
patients number 9 and 10 of the original 12 Sarepta 
clinical trial participants. Before I speak, I 
think you should hear from them since they are two 
of the most important voices in the room today.
JACK WILLIS: My name is Jack Willis, and I am patient number 9 in the Sarepta trial.

NOLAN WILLIS: My name is Nolan Willis, and I am patient number 10 in the Sarepta trial.

JACK WILLIS: We have chosen to dedicate the last five years of our lives to this clinical trial, quite willingly. Since we have lost the ability to walk, we have been labeled as the failures of the eteplirsen trial. We come here today not only to show that we are not failures, but to claim victory.

NOLAN WILLIS: We claim victory because our lives improved while on drug. Our hearts and lungs performed normally. We had some increase in strength. We noticed when we had to skip a dose we are more tired and lethargic. We know this drug will keep us alive longer.

JACK WILLIS: Duchenne patients don't die from not walking, they die from heart and lung failure. We are almost 15 years old with normal function, something which is not necessarily normal for other Duchenne kids our age. We did not have
one side effect while we have been on eteplirsen.

NOLAN WILLIS: We are not outliers. We have followed the natural progression of Duchenne, which has now changed due to eteplirsen. Even though we stopped walking four years ago, we are still able to pick books off the table, feed ourselves independently, drink without a straw, and brush our teeth without help.

JACK WILLIS: We are not failures because we stopped walking. Please stop calling us that. This drug not only preserves the ambulation -- this drug is not only to preserve ambulation, like we said. You don't die from Duchenne by not being able to walk. Maybe had we been on drug sooner, we would still be walking. Why would you make other boys wait when this drug could allow them to walk longer, to feed themselves longer, to hug their parents longer, to live longer?

MS. DWYER WILLIS: I was nervous that the boys would not qualify for this trial knowing that Nolan's ambulation was already rapidly declining. Our goal for this trial was not to preserve
ambulation. It was to preserve their quality of life and allow them to live longer, period.

Nolan took his last steps in February of 2012 and Jack joined him in June of that year. They fought hard to stay on their feet as their walking days were really gone before they even started the trial.

My boys became known as the kids who were making the data messy, who declined in the 6-minute walk test, who lost ambulation, and everyone began to question if the drug was working.

My boys make the data stronger because they are responders, they are making dystrophin. The drug is working in them. The production of dystrophin has changed the trajectory of their disease. My boys regained some upper arm and torso strength, were less fatigued, and regained some of their independence that had been lost.

In their case, loss of ability to walk independently has still not preceded a decline in pulmonary function. Thanks to eteplirsen, both of my boys are experiencing a clear deviation from the
natural disease course. My sons should give the ad comm panel members confidence that the drug is working in both ambulatory and non-ambulatory boys. Both populations will benefit from the approval of eteplirsen. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 33 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. JOHNSON: Our travel was supported by the Make Duchenne History Coalition. My name is Alex Johnson, and I have come here with 42 parents from Britain who have children with Duchenne. We've traveled all this way for 0.9 percent of dystrophin.

If eteplirsen gets rightly approved, we would move our family here for 0.9 percent of dystrophin. For those who were disappointed by 0.9 of dystrophin or don't know Duchenne well, this may be viewed as an act of desperation. Although the U.S. seems nice enough, we assure you, we would not
uproot our entire lives for something trivial.

Our decision rests firmly on scientific research. It is well-known in the scientific community that some exon 44 patients have spontaneous exon skipping that results in revertant fibers. This small amount of dystrophin leads to a slower disease progression.

Just two days ago, the Bello paper was published revealing that exon 44 patients have a later median loss of ambulation than other deletions on a Kaplan-Meier analysis. Two years more walking is life changing for patients and families.

MR. JOHNSON: The FDA calls into question Sarepta's use of a matched natural history control. They claim that the placebo arm of the drisapersen study is a more appropriate control. Most of that data came from European patients.

We know there is data from that study for a duration of 2 and a half years, but the FDA has only referenced the first year of data, then looks to other natural history studies on an apparent
hunt for a comparator group that appears to

diminish eteplirsen's effects.

We would like to know when using these
untreated cohorts, such as the CINRG data presented
today as a comparator, did the agency apply the
appropriate filters, such as age greater than 7 and
baseline 6-minute walk score, to ensure the closest
possible apples to apples comparison.

MS. JOHNSON: We know that being in a trial
can incentivize functional improvement. Maybe at
first, these boys on this study were influenced by
what the briefing document describes as expectation
bias, motivation, and coaching. Maybe.

But this is Duchenne we're talking about,
and we want the panel to know that every parent
motivates their child to keep walking. Every
parent loses that fight. Every parent, except
those of the 10 out of 12 boys on this study; yes,
they were motivated, but motivation alone cannot
account [mic off].

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 34 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. FURLONG: My name is Pat Furlong, and I am president and CEO of Parent Project Muscular Dystrophy. I have nothing financial to disclose.

On Friday, April 29th, my son Patrick died. He was just 15. He was Billy Ellsworth's age. He stopped walking at 9, and at the time of his death, he couldn't lift his hand to his mouth.

I spent those last nights with him attempting to remove secretions from pneumonia. It felt like I was suctioning concrete through a straw. Patrick was tired, and he tried to smile, but we knew it was goodbye.

Like my son Christopher, who died 7 months earlier on September 29th, Patrick had no options. None. Christopher and Patrick followed the predicted natural history. They were off their feet at 10 years old, and they died in their teens.

Today we're talking about a drug with significant great impact, one that is focused on
the fundamental defect in Duchenne, restoring
dystrophin. Eteplirsen is safe. Four years of
safety data with no adverse effects, no SAEs, none
whatsoever. We can argue small numbers. We can
argue about the quantification of dystrophin.

What is critical to discuss is the impact of
an incremental effect. A positive incremental
effect has a ripple effect across a lifetime.
Extending ambulation, preventing scoliosis,
delaying the need for ventilation, improving family
stability, decreasing the financial impact in terms
of accommodation, school, home, employment, and
most of all, improving and preserving the quality
of life.

We've done a benefit-risk study about
incremental benefit. The overwhelming priority of
the parents that participated was slowing disease
progression. These are important milestones,
measures of intermediate endpoints that should
serve as a future reference point for all
regulators and developers.

Your goal, the FDA, is to improve how an
individual feels, functions, and survives. If you ask these boys, I think they would say absolutely to that. So that's going to require considerable flexibility for all rare disease assessments.

Congress agreed and provided tools such as accelerated approval. In addition, they told you to listen to the patient voice. Inclusion of the patient in decision making and those choices will be best be heard via the more creative approaches to rare disease development, which better capture patient centered outcomes.

Patient-focused tools are of limited value if we continue to operate in a rigid and adversarial manner. Today, I'm asking for a paradigm shift for all parties, FDA and industry, to commit themselves to a fundamentally collaborative approach, both in this eteplirsen decision and in hopefully the many future INDs and DNAs that come before you. I urge the committee to exercise maximal flexibility. [mic off].

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 35 please introduce yourself? Please state your name and any organization you are representing for the record. Once again, please hold your applause until all speakers have finished.

MS. KELLY: My name is Melanie Kelly, and I have two sons with Duchenne muscular dystrophy, Jacob and Liam.

MR. KELLY: My name is John Kelly. I'm Melanie's husband.

MS. STELLY: My name is Trina Stelly. I have one son who is 12 with Duchenne, and I have an 8-year-old daughter who is a manifesting carrier.

MS. PEASE: My name is Katherine Pease. I have one son 8 years old with Duchenne muscular dystrophy.

MR. DENER: My name is Brian Denger. Our group represents those who are amenable in this therapy and relive the agony of missing the threshold for inclusion in this clinical trial. We are living the history of Duchenne muscular dystrophy.

We read in the briefing documents how FDA is
not impressed by the slowed progress of the eteplirsen patients because boys with Duchenne can lose ambulation between ages 8 and 18. We are concerned the reviewers are confusing something that is possible with something that is common. Are there outliers who are walking at 18? Yes. Is it common? No.

I have two sons affected by Duchenne. Matthew stopped walking at 8. His was a steady decline in physical ability leaving him unable to perform activities of daily living by 12. He succumbed to heart failure at 20.

His brother, Patrick, who is now 21, stopped walking at age 13. Though he walked longer, his progression followed the same path as his brother, just several years later.

We long came to appreciate that preserving function would be important and a life changing breakthrough. The difference in being able to walk longer, Patrick did at age 13, meant he didn't need spinal fusion surgery, unlike his brother who stopped walking at 8 and needed surgery at 13.
The level of ability of participants in Sarepta's trial exhibit is far different than what any of our sons experienced. Walking independently at 14, 15 is not the norm for someone who has Duchenne. These patients are walking well.

If you witnessed the last months of walking for someone with Duchenne, you'd realize how starkly different this truly is. In the final year of walking, not only do patients tire and have a significantly slower pace, but they fall, and they fall hard regularly.

Nearing the end, they need someone to help them stand, hold them upright while they find their balance, only to walk a meter or 2, not 6 minutes, before collapsing into a heap and wait to be picked up. No amount of motivation stops that tree from falling. That's not the same experience we see for the boys in the study. They walk with more balance and confidence.

We represent the patients who are amenable to this drug, and not one of our boys walked past the age of 13. As a parent who has lost a son to
Duchenne, I don't need a reminder of how time passes so quickly. We wait and watch as function is lost never to be regained. Each of us asks, how much longer. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 36 please introduce yourself. Please state your name and any organization you are representing for the record.

DR. NELSON: My name is Stanley Nelson. I'm a professor of human genetics and co-director of the Center for Duchenne Muscular Dystrophy at UCLA, and I have no financial interest in the outcome of the meeting today. I care for children with Duchenne and am an expert in genetic and genetic modifiers. I've served on clinical trials, data monitoring committees, and advisory boards related to Duchenne.

DuchenneConnect is the largest online registry, and in 2014, my group published a multivariate analysis looking at all 78 parameters collected and identified that the most strong
correlate with age at loss of ambulation was by far
the use of steroids. This is using a hard endpoint
of age at loss of ambulation. There was a minor
difference between daily deflazacort usage and
daily prednisone.

I'll also comment that the effect of LTBP4,
which was brought up by Glen Nuckolls on the
advisory committee, would be of minor concern in
comparing these sample sets, partly because the
LTBP4 allele, the haplotype, seen in a homozygous
state would only be present in about 10 percent,
and the effect of LTBP4 observed in three
independent studies is much smaller than the effect
observed by steroids, so controlling for steroids
is most important.

I can also give you a little bit of a
personal take in terms of the hard point of loss of
ambulation. I'm also here as the father of Dillon,
age 15, living with Duchenne. He lost his ability
to walk at age 13 and a half. Most boys that I
know socially, and Dillon in particular, are very
resistant to this transition and fight hard to push
it back as long as possible.

This is the case for Dillon and makes age at
loss of ambulation actually a rather hard endpoint.
You can change it by weeks, maybe months; extending
it longer is actually very difficult to do. It
makes it also an irreversible and highly
undesirable endpoint with substantial consequences
to his environment and care needs.

I know this well, and this point has been
brought up by several in the open public hearing
and in the Sarepta presentation, that Dillon lost
ambulation at 13 and a half and is therefore on the
slightly more mild end of Duchenne, and that's
supported by multiple natural history data. And
yet, when he was 9, his 6-minute walk distance, as
determined by being in a different clinical trial,
would have compelled him not to be a part of this
clinical trial.

So the boys that are at the outlier end,
those boys that are still walking at age 14, 15,
16, also tend to have better physical measurements
at ages 7, 8, 9 and 10, the exact group that
Sarepta was hoping to exclude from this.

I'll also note that many of these opinions were shared in a letter drafted by 36 experts in Duchenne that actually do support that there is substantial evidence of efficacy for eteplirsen based on the clinical data and based on the reasonable comparison to multiple external data sets. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 37 please introduce yourself? Please state your name and any organization you are representing for the record.

MR. PROCKO: We are Bill and Kim Procko, and thank you to CureDuchenne for our travel and lodging arrangements. Our son, Evan, is one of the original 12 participants. During the course of this trial, we have observed profoundly positive changes to his physical condition, each one of them contradicting normal Duchenne disease progression. Here is what 0.9 percent can do.

Natural history suggests that once a boy
with Duchenne loses the ability to get up off the
to the next 12 to 24 months. Evan remains walking
3 years and 2 months after losing this ability.

Prior to eteplirsen, Evan slept fitfully through the night, his fists clenched so tightly we
could hardly pry his fingers open, his calves in
full contracture. After eteplirsen, Evan's sleep became relaxed, his palms open, calves soft,
without contracture. Evan's body now rests and
recovers at night as it should.

Prior to eteplirsen, Evan fell 2 to 3 times per week. During the course of this trial, Evan's fall frequency has reduced to 1 fall every 2 to
3 weeks. The amount of Evan's daily walking has remained nearly the same.

Prior to eteplirsen, Evan's digestive process was noticeably slower than it is today,
with bowel movements 3 to 4 days apart requiring laxatives. At present, bowel movements occur daily without aid. His diet has always been healthy.
The only change has been eteplirsen.
On September 6, 2015, Evan suffered a spiral fracture to his right tibia. We knew that a broken leg and subsequent muscle atrophy from weeks in a cast for a 12-year-old with Duchenne more often than now spells the permanent end of ambulation. For Evan, however, after 7 weeks in a cast and boot, he stood up and walked unassisted.

According to his UF Schanz orthopedic staff, recovery time was indistinguishable from any non-Duchenne patient, and on November 2nd, only 8 weeks after his fracture, Evan was back in Ohio performing two successful 6-minute walk tests for Sarepta.

These observations contradict Duchenne progression. In the last four years, we've done nothing out of the ordinary concerning protocol with Evan's care except for eteplirsen. The FDA's January briefing documents stated that the boys in our study have received intensive physical therapy. The date of Evan's last physical therapy appointment was May 13, 2009. At home, we do a set of stretches 4 to 5 times per week. If anything,
this falls below recommended PT regimen.

MS. PROCKO: The benefits we have presented from 0.9 percent dystrophin are significant to us. Now, I wonder how many more years does that 0.9 percent give Evan independence to pour more hot sauce on his burrito or to wrap his arms around me in a hug.

Duchenne has taken away Evan's dystrophin. Eteplirsen has given him some back. Now, it's in your hands to allow him to keep it or take it away from him again.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 38 please introduce yourself? Please state your name and any organization you are representing for the record.

MS. PENROD: My name is Marissa Penrod, and my son Joseph has Duchenne. My son and the sons of the parents standing with me here right now are waiting for a treatment. This was a significant year for Joseph. It was the year that Duchenne stole Joseph's ability to walk. I assure you, he
had no choice. He wanted desperately to keep walking. It was not a question of motivation or mindset. Joseph lost ambulation because he has Duchenne.

We tend to think of loss of ambulation as the end of something, the end of walking, but really it's just a new beginning. It's the beginning of a new kind of decline. Decline in Duchenne comes in many forms. Dave and Maria's son Ryan, and Kelly's son Jack, demonstrate the immense burden of Duchenne through their struggle with self-image.

Anessa's teenage son, Tyler, can no longer go to his friend's house because they're not accessible. Natalie's son, Max, can no longer move his arms to scratch his own face. And Kat's [ph] son, Dusty, has just 12 percent of his lung function remaining. He is literally on his last breaths.

I know that Joseph's arm strength will go next. He won't be able to feed himself. I will have to hold a book for him to read, and hugs will
be a memory. We will face scoliosis, spinal surgery, pulmonary distress, heart failure. The loss of ambulation matters, but what matters more than losing ambulation is maintaining ambulation.

Thanks goodness for eteplirsen. Today should not be a day for uncertainty or fear, it should be a day of celebration. We know that many clinical trials and potential treatments comes with risk. Not this one. We know that some decisions you have to make are clouded by uncertain clinical benefits. Not this one.

Today we should celebrate and honor the truth, and we must not be distracted from that truth. Four years later, 4 biopsies later, that surgery under general anesthesia, they're still walking. How much more will you ask of them? When will their sacrifice be enough?

The FDA gave guidance to Sarepta in April of 2014 urging them to identify matched natural history cohorts. You can't move the target now, it is too late and our sons deserve better. Our kids are not your science experiment. They're not a
sample or a cohort or a subject. They're someone's brother and son, someone's grandson, and student, and best friend. Our children are not here to serve the science, but the science must always serve our children, and eteplirsen does that.

If not you to acknowledge the evidence that eteplirsen works, if you not honor the tools give to you by Congress and FDASIA to demonstrate flexibility, then who will? It's time to stop talking about flexibility and to show us. We don't hope you do the right thing, we expect you to do the right thing, and the right thing is to say yes.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 39 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. JUHASZ: Hello. My name is Rose Juhasz, from the University of Michigan Medical School, support by Make Duchenne History. My son is in the confirmatory study control arm amenable to exon 53 skipping. My comments today are coming both as a
parent and as an academic colleague who has worked
for nearly 15 years in the study and support of
personalized medicine. I currently manage a
$13 million NCI research program on precision
medicine in early stage breast cancer.

I could stress that precision medicine is
also here to treat children, and that we do so by
skipping exons. Instead, I refer you to a recent
JAMA neurology viewpoint by noted clinician
scientist Eva Feldman. She concluded, and I quote,
"Exon skipping offers tremendous promise, and the
impact on Duchenne patients may alter the practice
of neuromuscular medicine by bringing personalized
genetic therapies."

I could praise the FDA's accelerated
approval paths for select treatments in early stage
breast cancer. It's helped to render that disease
highly survivable and rich with treatments. We
desire similar flexibility for just a first
treatment in Duchenne. Without it, this is
disparity, and our children deserve better.

As today is about children, I'll share on a
clinical cohort I find relevant. Completing my own doctoral work, I had the privilege to study some of the first deaf kids to receive cochlear implants. They were implanted at relatively old ages after prolonged auditory deprivation. The FDA did not initially favor implanting kids earlier despite known critical periods for speech and language and preserving auditory function.

Positive outcomes in those first kids were not immediate. Those who did respond needed years of device use. For others, it was too late to get full benefit from a technology now known as groundbreaking.

Those were children failed by the FDA process. The technology was there for years; access was delayed. These are kids who will then live out the rest of their lives knowing that the quality of life could have been quite different had it not been for regulatory disparities and delays for children. Despite those odds and having received the first devices, there were some stand out responders. They became known in our research
group as the stars.

Today you have met the stars of exon skipping. They have walked up here and stood and told you that this drug is working and important for them. And as I stand here 15 years later, please hear this message.

No child should have waited then for the chance to hear, and no child today should be waiting this long to keep walking or to continue to use his limbs. This is a fatal disease. We cannot afford to fail them. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 40 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. SHIEH: Good afternoon. Yes, my name is Dr. Perry Shieh, and I'm an associate professor of neurology at UCLA, where I serve as the clinic director of the muscular dystrophy clinic. I would like to ask if somebody could pull up the slides for speaker number 36.
It's through this clinic that I currently care for approximately 100 boys and men with Duchenne muscular dystrophy.

DR. ALEXANDER: I'm sorry, we're unable to provide those slides at this time.

DR. SHIEH: Okay. That's fine. And I'm also an investigator in numerous clinical trials for Duchenne muscular dystrophy, including three ongoing clinical trials involving eteplirsen. I think the most important question today is whether eteplirsen works. Is whether eteplirsen clinically improves Duchenne muscular dystrophy patients. And I do like to thank the FDA for their caution and their extensive discussion about the potential shortcomings of the study data.

Nonetheless, I would like to emphasize that the study data do show reasonable substantial evidence of efficacy. I would like to echo the opinions of my colleagues before me that loss of ambulation is truly a hard endpoint. It is not something that is optional.

Generally, people who are not able to do
6-minute walk test will not be able to do anything very soon. And looking at the study data, looking at loss of ambulation as a function of a drug exposure seems to be the most appropriate way to analyze the data because baseline characteristics and baseline 6-minute walk tests do predict the future outcome, the future course of these boys.

Now, one may argue that the 4-year data was not blinded. It was not a placebo-controlled study. However, this is an issue of perhaps placebo effect, and many publications have indicated in the past that placebo effect is generally small, temporary, and relatively subjective.

The placebo effect would not prevent Duchenne boys, based on a hard endpoint such as loss of ambulation, from losing ambulation. Placebo effect cannot prevent them from losing the ability to walk. In fact, I believe it is the collection of study data over four years of this very progressive disease that makes this data very convincing and robust, and it would not be possible
to perform the double-blind placebo-controlled
study over the same amount of time.

So although 12 patients may seem like a
relatively small number for a clinical trial, the
effect observed is still impressive. Of course, we
would like the sponsor to complete the confirmatory
studies that are already ongoing that will have
many more patients, but the data have presented so
far are persuasive, and additional safety data from
ongoing studies, I do not believe that there's any
reason to limit access to this medication.

In other words, I would like to be able to
prescribe this medication to other Duchenne boys
who are amenable exon 51 skipping. The risk of
harm appears to be minimal. And with close
monitoring, I believe this is the best way to
acquire additional information about this effective
treatment. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 41 please introduce yourself? Please state
your name and any organization you are representing
DR. MCNALLY: Thank you. My name is Elizabeth McNally. I am a physician and scientist. I direct the Center for Genetic Medicine at Northwestern University in Chicago. I'm also a cardiologist who specializes in providing care for those with neuromuscular disease.

I'm a physician in the Muscular Dystrophy Association Clinic at Northwestern Medicine, where I work closely with neurology and pulmonary experts caring for those with advanced Duchenne muscular dystrophy. I have no consulting relationship with Sarepta. I have no bias in looking at the data here today.

Boys with DMD grow to be men with DMD, and they should not be forgotten here today in this discussion. There's been much focus and emphasis on walking as an endpoint in DMD, but walking is not an endpoint for a young man with DMD.

Retaining upper limb strength is important for being able to eat, drive a wheelchair, type on a keyboard, and hold a job. These are the
endpoints that matter. Walking is a surrogate for what happens to many muscles in DMD.

We know well from the earliest genetic DMD studies that the amount and quality of dystrophin production is the primary determinant of outcome in this disease. Dystrophin production linearly correlates with outcome. There has never been shown to be a threshold effect under which dystrophin level does not matter. Any increase in dystrophin is meaningful.

The goal of exon skipping is to convert the more severe form of disease, DMD, to the milder form of disease, Becker muscular dystrophy, but what does that really mean?

I think of the many DMD guys I take care of. I think of Ryan and I think of Joe in particular. They have DMD. They went to college, they graduated, but it was hard to find work with the fact that they had lost so much upper limb strength, and post-college life has been hard for them. With even modest improvement in upper arm strength, they would be able to do so much more.
I am also a scientist and an established investigator in the neuromuscular field for more than 20 years. As a scientist, the FDA conclusions regarding dystrophin quantitation presentation are most puzzling. We heard that three independent veterinary pathologists arrived at different quantitative values than the pathologist from Nationwide Children's Hospital, and based on this discrepancy, the immunofluorescence results were devalued.

The dismissal of the immunofluorescence data seems to be skipping the critical point that these veterinary pathologists identified a clear difference between treated and untreated patients, 17 percent versus less than 1 percent.

It is implied that immunoblotting is somehow superior to immunofluorescence microscopy, and this is plainly inaccurate. Blotting methods are hampered by the large size of dystrophin, its high susceptibility to proteolysis, and the challenges in extracting dystrophin adequately from fibrotic muscle.
Blotting fails to take into account for the regional distribution of dystrophin expression within a muscle. To be fair and unbiased, both blotting and fluorescence methods should be considered together.

Today, we saw data that eteplirsen treated boys walk longer, walk farther, have more dystrophin on blotting, and on fluorescence. Moreover, this drug is safe. It seems prudent to recommend accelerated approval based on the data.

(Applause.)

DR. ALEXANDER: Thank you. Will speakers number 42 introduce yourselves? Please state your name and any organization you are representing for the record.

MR. MARQUEZ: My name is Ethan Marquez. I am joined by Kadee Roden, Christina Burrell, and Sandra Katzin. Each one of us has a son with Duchenne muscular dystrophy and enrolled in the confirmatory trial of eteplirsen.

Our boys are between the age of 10 and 13 years old and have been taking eteplirsen for
approximately one year. We all have noticed our boys doing things they weren't able to do before the trial, and I'm here to share our stories.

Before eteplirsen, Sandra's son, Ethan, was extremely lethargic, unable to walk for long distances. Today, he can walk alongside his mother without getting exhausted. His stride is more stable. He does not fall as much as he used to.

This is important to note because a reduction of Duchenne falls is a commonly reported result of eteplirsen. This is a massive quality of life improvement because it means he is less likely to fall and injure himself.

Christina's son, Xavier, and Kadee's son, Morgan, have also experienced an increase in strength since being on eteplirsen. Since starting the trial, they have the ability to keep up with their friends at school and not come home exhausted. Xavier can independently dress himself, comb his hair, put on his shoes.

DR. ALEXANDER: I'm sorry for interrupting. If you're having conversations, can you please have
those outside.

MR. MARQUEZ: Tie his shoes, and even brush his teeth. These are daily tasks that he could not do before eteplirsen. Since my son, Peyton, started on eteplirsen over a year ago, my wife and I have seen him stabilize, gain his strength, and even move in ways he has never done before. This has not happened to a boy with Duchenne. We've all seen eteplirsen working.

Before starting the trial, Peyton could not kick his foot above the air, now he can kick his foot above his waist.

(Laughter.)

MR. MARQUEZ: Before eteplirsen, he was unable to pull himself out of our pool. He would just barely hang onto the edge. Now he can pull himself out. He used to struggle to climb into our SUV and onto his bed, now he can do both with ease. Before he came home exhausted and needed a nap. Now he has the stamina to participate all day in school and after school activities, and even stay awake until bedtime.
Eteplirsen has given us hope for his future. We no longer plan his funeral. Now, when Peyton talks about driving, attending college and becoming a scientist, because of eteplirsen, we believe it's possible.

I implore you, recommend this drug. It is clear to us, our sons, our children's teachers, family and friends that eteplirsen works. It is safe and needs approval so many of the boys have a chance. We already know the results without eteplirsen.

This committee has the ability to recommend that the FDA approve a drug that will improve the quality of life for our entire community. It will lead to other breakthroughs. To not approve it for many other boys that are suffering, that have suffered, and that will suffer in the future is not only confusing but outright cruel. Substantial evidence of the effectiveness of eteplirsen is clear. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 43 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. CHAMBERLAIN: My name is Jeff Chamberlain, and I'm a professor of neurology at the University of Washington. I'm also director of the Senator Paul D. Wellstone Muscular Dystrophy Research Center, and I'm a paid member of the Sarepta scientific advisory board.

I've been studying the molecular genetics of DMD for 30 years with a focus on dystrophin expression and the development of gene therapy. For these goals, my lab has developed transgenic mice, we've developed adenoviral vectors, lentiviral vectors, and AAV vectors in order to study how much dystrophin is needed to prevent or to reverse the pathophysiology of DMD.

We've also been looking at the relative effects of producing full length Becker-like and micro dystrophin proteins in muscle. These studies have been remarkably consistent in showing that very low levels of dystrophin can have significant
effects on muscle function.

Now, it was mentioned earlier that dystrophin levels as low as 10 percent of normal can prevent and largely reverse the dystrophic pathology, and our data and animal models certainly agrees with that. However, those levels are essentially what are needed for a cure, and we're not here today talking about a curative therapy. It's very important to emphasize that our studies of animal models also showed that much lower levels of dystrophin have a clear and measurable impact on muscle function, and this is true whether we're expressing full length dystrophin, Becker-like dystrophins, or even the micro dystrophins that were developed in my laboratory.

Our studies of dystrophin function have also demonstrated a mechanical role mediating the lateral transmission of force from within a myofiber into the extracellular matrix. And the consequence of this is that a single dystrophin positive myofiber has a clear protective effect on
adjacent dystrophin negative myofibers.

Thus, the overall protection that's conferred by low dystrophin expression is greater than what you would predict by a simple comparison to normal dystrophin levels, and it's greater than you would see just by looking at the percent of dystrophin positive fibers. We have clear data that even a single dystrophin positive fiber protects adjacent fibers, so patchy or mosaic expression of dystrophin has a wider effect than just counting dystrophin positive fibers. In fact, our studies indicate that any dystrophin expression has a beneficial effect on overall muscle function and physiology.

In summary, our data in animal models acquired through a variety of different methods predict that the dystrophin expression patterns that have been observed with eteplirsen are sufficient to achieve a significant increase in muscle function. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much.
Because we're running over, I'd like to take a break now. So we'll take the afternoon break at this time. So this is going to substitute for the break that would be coming up at the end of the open public hearing. So we'll take a 15-minute break at this time. Thus, we'll come back at 10 minutes after 5, 5:10.

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 5:10.

(Whereupon, at 4:55 p.m., a recess was taken.)

DR. ALEXANDER: If you can please take your seats. We're going to be beginning in just a minute with open public hearing speaker number 44 in just a minute.

(Pause.)

DR. ALEXANDER: Okay. Out of respect for those public speakers, if you are still conversing and wish to continue, please do so in the hallways. And we'll be beginning now where we left off which
is with speaker number 44.

If speaker number 44 could introduce
yourself, please state your name or any
organization you are representing for the record.

MR. WOLF: We appreciate the break, but you
can't ice this kicker so thank you.

I'm Brian Wolf, and I am joined by exon 45
and 53 waiting group, and our travels was arranged
by the Make Duchenne History Coalition.

Our group consists of Amy Aikens,
Chris Daimler and Cindy Quitzau. We represent
Duchenne patients in need of access to follow-on
drugs, specifically exon skipping 45 and 53, and we
fully support the approval of eteplirsen.

We are here to support our Duchenne
community for exon skipping 51 and believe that
future exon skipping drugs will advance with the
approval of this first drug. While we wait, our
sons continue to get weaker and we are running out
of time.

Four and a half years ago, we began to hear
and see the stories of continued ambulation and
increased flexibility and zero side effects in the patients in the eteplirsen 201/202 trial aside from their encouragement. We also see the publicly released data and were encouraged by eteplirsen's unprecedented results. We need to include the rest of our Duchenne family in this huge vehicle of hope.

The approval of eteplirsen would be our first critical step in getting this new life-saving technology in the hands of other Duchenne patients, including our sons. The FDA has the authority to approve this drug next month and make a meaningful difference in the lives of families.

As parents, we have become advocates, speakers, caregivers, educators, and fighters, and we have passed those traits to our sons and daughters, those with Duchenne and those without. Despite how the media sometimes portrays us, we are not desperate parents. We are educated in the data, the expert scientists and clinicians support us, and we are not willing to give our children a drug that isn't safe or doesn't work.
The FDA in this division have wavered with their guidance far too many times, which in turn has delayed the opportunity for our sons to receive the needed exon skipping drug. Today, you have renewed opportunity to follow FDASIA and use the tools Congress has provided FDA to expedite access of life-saving treatments to patients who need them.

Today, we ask the committee to consider the total and quality of eteplirsen's data and the patient and expert testimony and please, recommend eteplirsen for accelerated approval.

Our community has already experienced many unnecessary delays related to this drug. Do not waste any additional time so that thousands of other waiting Duchenne patients from our group that we represent can make Duchenne history by outliving their diagnosis. Thank you.

DR. ALEXANDER: Thank you very much.

(Applause.)

Will speaker number 45 please come to the podium and introduce yourself? Please state your
name and any organization you are representing for the record.

MR. KUNKEL: Yes. My name is Lou Kunkel from Boston Children's Hospital in Boston, in the Department of Genetics and Pediatrics at Harvard Medical School. I am a paid member of Sarepta's scientific advisory board, and my travel here was paid for by Make Duchenne History Consortium.

My laboratory was the laboratory which identified the gene responsible for Duchenne dystrophy back in 1986. In 1987, we described the encoded protein, dystrophin, and we showed that major mutations at this two-and-a-half megabase locus were deletions in both the severe Duchenne form of dystrophy, as well as the milder form of Becker muscular dystrophy.

We proposed, at the time, that the difference between deletions in Duchenne patients and Becker patients were based on the effect they had on the translational reading frame of the encoded protein. We predicted Duchenne patients would make no protein because they would have
premature stop because they've disturbed the reading frame, whereas Becker patients would have an internally truncated protein but that it would be made.

We showed, in 1988, that protein was not being made in Duchenne biopsies, published in the New England Journal of Medicine. And in that article, we talked about the limit of our detection. This is in 1988, and this is where this 3 percent number comes from.

Eric Hoffman used both myocin staining post-transfer to estimate underloaded gels and said that he couldn't probably see below 3 percent. But that's a long time ago, and the technology has changed a lot since then. Becker patients were shown to make an abnormal truncated protein of variable degrees of levels of the protein.

This led us to propose, as Steve Wilton did, that, potentially, we should try to block the inclusion of exons and convert a Duchenne into a Becker by interchanging the reading frame and producing protein.
Sarepta's eteplirsen is designed to block exon 51 in 13 percent of dystrophin deletion patients. They documented that exon skipping 51 is skipped based on RTPCR, so the mechanism of action of that drug is working. They document on immunofluorescence that the protein is being made, albeit at not quantifiable levels but way above what we've ever seen for revertant fibers.

But for me, the best evidence was their Western blots, which showed 0.9 percent. We never see 0.9 percent in patient biopsy samples, and so this is really an appreciable amount. Consistent with this was the clinical progression. These make dystrophin, its safe, and I believe there's no reason not to approve.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 47, please come to the podium and introduce yourself?

MS. LEFFLER: I'm 46.

DR. ALEXANDER: I'm sorry, 46. Will speaker 46, please introduce yourself? Thank you. Please
state your name and any organization you are representing for the record.

MS. LEFFLER: My name is Mindy Leffler, and I'm here representing my family. We are listening to two versions of reality today: Sarepta's is that a group of boys who are on the cusp of decline, took an experimental drug, and progressed slower than expected. The FDA's is a group of boys with DMD who frequently walked past the age of 13. Sarepta lucked into a group of them, and everything else you're hearing today in support of efficacy is either wishful thinking or coincidence.

Here is my son's story, and you can decide which it supports. Aiden screened for the study we're evaluating today. He walked too far to fit the inclusion criteria and he was not included. We went with plan B, which ended up being the placebo arm for drisapersen, the very data set cited in FDA briefing documents as the most accurate control for eteplirsen.

So he was too functional for the eteplirsen study, and yet somehow he's the perfect control for
When Aiden was on driersperse, I relied on casual observation to draw my conclusions. By the time he was off drug, I had nothing definitive to say. So at age 11, when Aiden was put on eteplirsen, I was not going to rely on observation. I wanted to be objective about how he was doing because I didn't want him spending any more time on a drug that might not work.

I picked the things he struggled with the most: getting off the floor, going upstairs, getting in a car, and spontaneous collapsing. I took a video at regular intervals and I kept a daily log of collapses.

So I am not standing up here with anecdotes about how strong my son was on drug and simply asking you to trust me. I'm saying that I put together a perspective PRO program on Aiden when he started eteplirsen, and I captured data regularly in a rigorous way.

On eteplirsen, Aiden went from collapsing 2 to 5 times per day to not collapsing anymore, at
all. On eteplirsen, Aiden regained the ability to pull himself into the car independently for the first time in over a year. As of this morning, he can still do it. I would challenge anyone to find that kind of progression, regaining definitively lost milestones anywhere in the natural history of Duchenne.

The briefing documents spend a great deal of time criticizing each piece of data independently, but if you look at the data as a whole, either eteplirsen works or there are a whole lot of coincidences pointing in the same direction.

Medical students are often told when they hoof beats to think of horses, not zebras; look to the obvious conclusion rather than searching for the unlikely. It is now time to stop hunting zebras.

(Appause.)

DR. ALEXANDER: Thank you. Please hold your applause until the last speaker has spoken. Will speaker 47 please introduce yourself? Please state your name and any organization you are representing
DR. DAY: Yes. My name is John Day. I'm a professor of neurology and pediatrics at Stanford University. And I appreciate having the opportunity to address the advisory committee to provide my perspective on the importance of making eteplirsen available for treating Duchenne.

I've received financial support from Sarepta for scientific consultation. My travel to the meeting was supported by the Make Duchenne History Coalition, but I have no direct financial interest in the outcome of today's meeting.

I direct the Stanford Neuromuscular Program, Stanford Duchenne Comprehensive Care Center, where we see Duchenne patients from a large part of Northern California. For the preceding two decades before moving to Stanford, I was director of the neuromuscular program, the Paul and Sheila Wellstone Muscular Dystrophy Center, and the Duchenne Comprehensive Care Center at the University of Minnesota, where I saw patients from the Upper Midwest and where I also ran my own CLIA
certified neuromuscular biopsy lab.

I've rewritten my talks to basically focus on specific issues the FDA brought up in their review, so I won't be needing any of the slides.

First, regarding the adequacy of the control group, it matches my own experience. During the course of my career, I've diagnosed and cared for 250 boys with Duchenne muscular dystrophy, more than 20 of whom had exon 51 skippable mutations. Despite optimal care, none of those boys walked beyond 12 years of age. This clearly differs from the eteplirsen 201/202 experience where boys continued to walk for 3 to 4 years of treatment at ages greater than 12.

In addition to my experience with Duchenne natural history, we have 4 subjects at Stanford involved in current eteplirsen studies, all have remained ambulatory, ages 9-11, and are functioning well in multiple respects with no side effects.

Second, in terms of questions regarding reliability of age of loss of ambulation, we can agree with Dr. Farkas' contention that a placebo
arm differs from a natural history study. But my experience is that boys try to keep walking as long as possible and that the difference of several years between walking and non-walking, by my experience, mirrors the results in the Italian registry, and the eteplirsen's results are striking and meaningful.

Furthermore, in a slide of speaker number 36, Stan Nelson, you can see a statistically significant difference in the Duchenne Connect data regarding the Kaplan-Meier curve for loss of function of eteplirsen compared to steroids alone.

In essence, I'm convinced that eteplirsen improves the course of Duchenne by multiple measures, and I strongly urge its approval.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 48 introduce yourself? Please state your name and any organization you are representing for the record.

MR. LOPEZ: My name is Roger Lopez, and I represent the International Association of
Firefighters as the IAFF MDA national coordinator.
We have no financial interest in this.

The IAFF is a nonprofit 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. Our members protect the communities that are home to over 85 percent of the population of the United States.

The IAFF is based in Washington, DC within a network over 3200 local affiliates. For over 60 years, the IAFF has stood shoulder-to-shoulder with the Muscular Dystrophy Association in the ongoing fight against the more than 40 neuromuscular diseases that are claiming the lives of our children and our fellow firefighters.

Through our Fill the Boot campaigns, the IAFF has helped MDA fund the research that is now resulting in the development of breakthrough therapies for these devastating diseases. To date, we are proud we have contributed over a half
billion dollars of funds to help find an end to diseases like Duchenne, $26 million just last year.

Our commitment to this fight is unwavering. This year alone, more than 162,000 of our firefighters volunteered their time in more than 3000 events across the country to raise money to support this mission.

But our hard work and dedication go beyond our commitment to fill the boot. We are in this fight at a personal level. Every year, many of our firefighters from around the country dedicate a week of their time to volunteer to MDA summer camps. These are wonderful places where kids can go to get a traditional summer camp experience despite the challenges they face.

Last summer, many of our firefighters had the chance to share the week with these amazing children. 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.

Through our many years of working with the MDA and the families they serve, we understood the
impact of this disease, and we want to see
effective options for every one with Duchenne and
the other related diseases become available.

I am not here today as an expert on the
science, but we as firefighters want to take this
opportunity to express our support for finding
therapies that can improve and save the lives of
the people that we love, people living with
muscular dystrophy.

We have helped lead this fight for more than
half a century, and we are proud of the IAFF's many
contributions, and will continue this fight to
fulfill the promise from our earliest days of our
partnership to join forces and fight back until
cures are found.

I have 16 seconds left, and I want to relate
to the families, how important you all are to us
and that we've been doing this for 60 years, and
we're here for you. And we're going to be here for
you until we find a cure. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will
speaker 49 please introduce yourself? Please state your name and any organization you are representing for the record.

DR. CWIK: Good afternoon, I'm Dr. Valerie Cwik, representing the Muscular Dystrophy Association. I have no personal financial relationship with the sponsor, but MDA receives contribution for educational support and conferences from a number of drug companies targeting therapies for muscular dystrophy, including Sarepta. And some of our board members, because they have expertise in this field, from time-to-time are paid to consult with drug companies, again including Sarepta.

I'm pleased to be here today on behalf of MDA and the thousands of Duchenne families that we represent. At the outset, I'd like to share MDA's optimism that there will soon be treatment options to change the course of Duchenne muscular dystrophy and that eteplirsen could be the first of what we hope will be many new treatments for MDA families.

As chief medical and scientific officer at
MDA and as a neurologist and former MDA care center director, I've worked with many families living with Duchenne. I'm reminded that my 25 years of medical specialty in the neuromuscular diseases is about the same amount of time that the average person with Duchenne can expect to survive, and this is a reality that is unacceptable to MDA.

MDA has led the search for treatments and cures for Duchenne for more than a half century and will continue to do so until there is a cure. Twenty years ago, we funded foundational exon skipping research and follow-on studies that led to the development of eteplirsen. And while not a cure, the data indicates that the drug could slow disease progression.

Many leaders in the Duchenne research and clinical communities have voiced enthusiastic support for eteplirsen, and as a science and evidence-based organization, their support carries great weight with us.

All of us at MDA, as well as our sister organizations, scientific community, families and
supporters have been working tirelessly to see a time like the present, a time when therapies could be more than just a hope for the future. We are all here for those living with Duchenne and the people who love them.

It is time that treatment options shift from being a goal to being reality. While the decision of whether to approve a drug is ultimately a regulatory science determination for the FDA, given the support of Duchenne scientific and clinical leaders, the support of the families we serve, the urgent and unmet medical need, and the strong safety data, we urge you to strongly consider all of the tools available to the FDA to allow the earliest possible access to eteplirsen. Thank you.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 50 introduce yourself? Please state your name and any organization you are representing for the record.

MS. HICKMAN: My name is Chelsie Hickman, and I'm reading a statement on behalf of
Shannon Dematteo, the mother of one of the 12 study participants who started in 2011.

"On March 3, 2008, at 5 years old, our son, Jack, was diagnosed with Duchenne muscular dystrophy. Jack's doctor never described him as an outlier, and as far as we could tell, he followed the normal progression of Duchenne.

"When Jack was 8 years old, we began traveling to Columbus, Ohio from Chicago every Sunday for a Monday infusion in the eteplirsen study.

"I've heard that the FDA thinks that the benefit that the boys in the trial with Jack may have seen was because they started steroids early or their steroid dose or standard of care was far better than those in the natural history group. But I would like to let you know that Jack started at age 6 and was dosed correctly for his weight. He received stretching as physical therapy every other week for about an hour and now swims once a week, neither of which could be described as a rigorous, intensive regiment."
"Never once, in the three-plus years of Jack receiving eteplirsen has he had an adverse reaction to it, not a fever, not a cough, not a headache, nothing. In fact, most of the time, we noticed that the day after his infusion is often one of the best days of his week as far as his energy level and his physical abilities.

"Because we understand Duchenne, we were fully prepared to be taking care of a child who was wheelchair-bound by the time he was 10 or 11. When Jack was 11, he was playing on the school's volleyball team.

"Our kids all go to Catholic school in a very old building that's not ADA accessible. He was able to walk up and down the stairs several times a day, every day in school, until he was in 5th grade.

"Jack, at 13 and a half, is still declining but at a much slower rate than we expected. He needs help getting up from the ground, and he uses a scooter or wheelchair to get around for distance. But for the majority of his life, he is completely
independent. Like all of the 7th graders in our neighborhood, he walks around with his friends to go to the park, out to eat or just to hang out. He's on the student council at school, is the assistant coach manager for every one of the school sports teams, and he has more friends than we can count.

"Because of eteplirsen, Jack has been able to enjoy a far more normal and active life than we ever could have dreamed. We thank God every day for our good fortune. We know Jack one of the lucky ones, and we know that other boys, like Jack, would benefit from being on this drug." Signed, Shannon and Tom Dematteo.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker 51 introduce yourself? Please state your name and any organization you are representing for the record.

MS. LEFFLER: I'm introducing my son's video testimony on his experiences on eteplirsen. We chose to have him submit video testimony because we
didn't want him to come here and realize that his access to eteplirsen was at risk.

Aiden, you see, is a warrior. In his testimony, you'll see a series of videos of Aiden trying to get into the car. At the start of the study, I did not tell Aiden how long it might take for eteplirsen to work because I did not want to bias his performance.

The first video was taken over a month into the study. Aiden is frustrated at this point because he is convinced that the drug doesn't work.

Two weeks after this video was taken, in fact, he asked me if he could quit the study because he was tired of hospitals and needles without seeing benefit.

Members of the advisory committee, please watch my son regain function with your own eyes. Ask yourself how it could be placebo-controlled or placebo effect if he is convinced the drug doesn't help.

Survey what you know about Duchenne and ask yourself how likely this video would be if
eteplirsen doesn't work. It is not enough to listen to our words and send us on our way. You are charged with using our words to inform the decisions that you make and hear our Aidens.

(Video played and transcribed.)

AIDEN LEFFLER: My name is Aiden and I'm 12 years old. I have Duchenne muscular dystrophy. I've been on eteplirsen for only a little over a year, 62 visits. I stopped being able to get myself into our car about 9 months before started eteplirsen.

I used to wait by the car door, and then mom would pick me up in the arms and lift me into the car. It's embarrassing at school being picked up like that in front of friends. And then it all changed.

I would like to show you some clips of how life has treated me since I started this drug, at the beginning of the trial, 5 months in and 7 months in. And it really has been changed.

(Pause.)

AIDEN LEFFLER: My mom was more than scared
I wasn't going to be able to walk anymore. But then I started eteplirsen, and now I'm able to do everything I was before.

Now, you'll see me downstairs playing soccer for hours at a time. Now, I can use the car ramp, now by myself. I taught myself. Thank you, eteplirsen. Thanks for giving me a chance to be normal, to do what I want to do.

I'd like to end my presentation with a video of me playing catch with Russell Wilson, quarterback with Seattle Seahawks.

(Laughter.)

AIDEN LEFFLER: Thanks to eteplirsen I'm able to enjoy moments like this, moments that every boy waiting for eteplirsen deserves.

(Applause.)

DR. ALEXANDER: Thank you very much. Our final speaker is speaker number 52. If you could introduce yourself. Please state your name and any organization you are representing for the record.

MS. McLINN: My name is Laura McLinn. I paid my own way here, and I have no financial
interest in today's outcome.

My 6-year-old son, Jordan, is a candidate for exon skipping, but is not yet able to receive the drug. On Thursday, I received a phone call from United State Senator, Joe Donnelly. He asked if I would read a letter that he and three other senators wanted to share with you today. He's in our home state of Indiana today and regrets that he cannot be here personally. I won't have time to read the entire letter, so I will share some key points.

"In 2012, Congress provided additional tools to facilitate new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially when no satisfactory alternative exists.

"We write today to underscore the focused efforts of Congress to provide for and encourage accelerated review of promising therapies, prioritize the patient perspective in evaluating new drugs and treatments, and provide regulators with flexibility to expedite evaluations of drugs
for life-threatening illnesses for not only Duchenne but all rare and severe diseases.

"FDA regulations state that it is appropriate to exercise the broadest flexibility in applying the statutory standards. As members of Congress, representing constituents who are battling rare and severe diseases with unmet medical needs, we wholeheartedly agree with this viewpoint and we urge the FDA to ensure this flexibility is applied in reviewing all candidate therapies.

"The cost of unnecessary delays manifests in terms of human lives. And therefore, urgency on this matter to patients and their families is absolute. Thank you for your attention to this important matter."

This is signed by four United States senators: Ron Johnson, Thomas Carper, Joe Donnelly, and Dan Coats.

As you know, there are similar letters from the United States Congress highlighting these points, especially the requirement that the FDA
consider the perspective of patients during regulatory discussions.

There seems to be a challenge with measuring dystrophin. That doesn't mean it's not there. It means maybe more work needs to be done in this area, right? I mean really, we don't have a true scientific piece of evidence that explains how we even exist but we do exist, right?

(Laughter.)

MS. McLINN: Do we need a piece of scientific evidence to proof the amount of dystrophin? Your evidence is right here in this room. And because of FDASIA, you are not only allowed to use that evidence, but you have a lawful and ethical responsibility to do so.

Every person in this room has been given a shot at this thing called life. We didn't deserve it, but God gave it to us anyway. There is no lawful, moral, scientific, or ethical reason to deny these well-deserved boys a chance to live their lives and fulfill their own destinies. Let's do the right thing. Let's make Duchenne history
Questions to Committee and Discussion

Dr. Alexander: Thank you very much, speaker, and for all the speakers that participated in the open public hearing. We'll 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 at the request of the panel.

I also want to remind the panel as there's an extraordinary amount of information that we could talk about and lots and lots of interesting areas for discussion, so please, keep your questions crisp. And for those that are responding to questions, either on the part of the FDA or the sponsor, please keep your answers crisp and concise as well. Thank you.

So we'll move to the first question at hand, which was provided to all of the panelists. The
The question itself is to discuss the evidence presented about dystrophin production, including the following: A) the strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients relative to their baseline; and B) the clinical meaning of the amount of dystrophin observed in the muscles of eteplirsen-treated patients, taking into the consideration the range of amounts of dystrophin known to be typically present in patients with DMD and in patients with Becker muscular dystrophy.

I'll also point the panelists, there is a little bit of discussion that precedes this actual question that's posed, if that's helpful for you to review again, but I think that we've heard the content of that in the presentations from both the sponsor and the FDA.

So with this, we'll open for discussion. The first question, which is a non-voting question, discuss the evidence presented about dystrophin production.

Dr. Green?
DR. GREEN: Okay. I think there is moderate evidence for dystrophin production. However, I think it's more difficult than that because at the end of the day, we don't really have a clue as to how much is clinically significant.

We also, at least I don't, have a clue about this dystrophin that's manufactured, whether it is effective, the same or better than native dystrophin. So I think it's a very difficult biomarker.

DR. ALEXANDER: Thank you. I'm sorry. Dr. Onyike?

DR. ONYIKE: If I recall from Dr. Farkas' testimony earlier, it would appear that there are some people who have very, very low levels of dystrophin and much better clinical function than you'd anticipate from that -- am I recalling that correctly?

So it seems to me, therefore, that there might not even exist the threshold of effect but rather, it's possible that dystrophin couples in some way that is indirect to function.
I recall that -- I think it was Dr. Chamberlain and the gentleman also, the investigator from Harvard, also suggested that the levels of -- that it might take very low levels to achieve a significant clinical effect.

Now, the question is whether that would be universal or whether it would only apply to a subset of individuals. And if so, what are the other markers that might indicate or that might predict how dystrophy links to clinical effect?

So in other words, it's ambiguous. I agree with Dr. Green in that sense, that it's very ambiguous.

DR. ALEXANDER: Thank you. And am I understanding you correctly that you're pointing out that it's ambiguous with regard to whether there's a threshold effect or not, but also was there a second part of that, what else may couple with the absolute amount of dystrophin to produce the clinical response that one sees?

DR. ONYIKE: Well, first of all, I suspect that there may not be threshold per se or that the
threshold may vary widely perhaps on an individual
or in the subgroup way, and that we have no idea
what that range is. But it may very well dip very
low.

Does that clarify?

DR. ALEXANDER: Yes, thank you.

Dr. Kesselheim?

DR. KESSELHEIM: To me, a lot of the answer
to this question of whether there's an increased
amount of dystrophin in the muscles depends to a
lot of extent on the methods being used to assay
that. I guess I wasn't convinced or I'm still
questioning whether the biopsies that were taken
were the correct biopsies and why it was that the
two different muscle groups were compared. And I
was dismayed by some of the inconsistencies and the
availability of the comparative evidence.

So I think that because of those various
things, it makes it pretty hard to draw a firm
conclusion about point A.

DR. ALEXANDER: Thank you. Other comments?

Dr. Hoffman?
DR. HOFFMAN: Yes. I think there's plenty of evidence that the mechanism of action for eteplirsen is producing dystrophin. Both the PCR testing, the immunofluorescence, and the Western blot all have indicated, many times in all different species, that mechanism of action.

DR. ALEXANDER: Thank you. Yes, I didn't hear Dr. Kesselheim or others question the mechanism of action. What I heard was that conclusions about whether or not there's a large amount produced depends upon the methods used to assess this, and also some concern regarding whether the biopsies were the correct biopsies or not and concern regarding the quality of the comparative evidence.

DR. HOFFMAN: I read the question as, is eteplirsen producing --

DR. ALEXANDER: Can you speak into the microphone more please?

DR. HOFFMAN: Yes. I think the question --

DR. ALEXANDER: I'm sorry. State your name also for the record.
DR. HOFFMAN: Yes. Richard Hoffman. I think there's plenty of evidence in all those different testing methods that show that the mechanism of action of eteplirsen is to skip exon 51 and produce dystrophin. I don't think there's any question about that. It's not only in humans but in other species.

DR. ALEXANDER: Thank you. Dr. Ovbiagele?

DR. OVBIAGELE: Perhaps I'm not reading this correctly, but as I understood it, one of the big challenges here was the issue of not enough pre- and post-treatment comparisons on the same patients; so no matched baselines. And that's exactly what the A question is asking.

So for me, there isn't the evidence there because the comparisons were with other controls but not necessarily the pre- and post. Is that correct?

DR. FARKAS: Yes, that's the concern.

DR. ALEXANDER: Thank you. I'm transcribing while we go. Other comments regarding question 1?

Ms. Gunvalson?
MS. GUNVALSON: I agree with Richard that --

DR. ALEXANDER: I'm sorry. Can you please state your name for the record?

MS. GUNVALSON: My name is Cheri Gunvalson, and I agree with Richard that the issue was to produce dystrophin, and we did produce dystrophin, or the drug did, as Dr. Kunkel said. And I believe we're seeing clear benefit from it. I know hundreds of boys with Duchenne, my son included, and you just don't see this clinical benefit.

DR. ALEXANDER: We will be discussing benefit, but for right now we're focused strictly on the dystrophin production in terms of the strength of evidence, that the drug increased the amount of dystrophin and also the clinical meaning of the amount produced.

So do you feel that the amount produced is sufficient to explain the clinical benefit?

MS. GUNVALSON: Yes, I do believe. And as the physician down there said, we don't know the exact amount. There are Becker boys that produce
very, very trace amounts that look very, very good.
We just don't know that.

So I don't -- for me, the fact that it
produced dystrophin and there are some boys and
young men with very scant amounts that do very
well, it's difficult to know the clinical benefit.

You know, I think we're all learning here,
not only the physicians and the FDA. This is a
learning process. There's never been a drug
approved. So that's my opinion.

DR. ALEXANDER: Thank you very much.

Dr. Woodcock?

DR. WOODCOCK: I would like to talk about
the order of this question. Question 1B, all
right, whether the clinical meaningfulness, you're
going to talk about that next as far as the
strength of the clinical data. However, what might
influence your assessment of whether the dystrophin
is actually clinically meaningful might be the
clinical data from the study or studies that were
done.

So if you're talking about this first,
you're going to have to think about what you think about the clinical studies in relation to the amount of dystrophin that has been produced, if you follow me.

DR. ALEXANDER: Thank you. Yes.

Dr. Kryscio?

DR. KRYSCIO: Yes, the other Richard, Richard Kryscio. Would like to ask Richard, since you know these measurement techniques a lot better than I do, where is the dose effect? I didn't see any dose effect when they looked at 50 versus 30.

DR. HOFFMAN: Well, you're talking about a dose ranging study, and really that hasn't been accomplished. Maybe there's not enough of a difference between 30 and 50 in animals. As far as I know, in mice, they've gone up to 900 milligrams per kilogram; and in dogs, I think they've gone up as high as 200 milligrams per kilogram. And I think at those higher doses, you would see the dose effect.

I think one of the problems here is it's been described by several people, the expression of
dystrophin in the muscle is regional or what's been
described as patchwork-type fashion that it's
produced after exon skipping. So if you're taking
a biopsy, it just represents a very, very small
part of the total musculature. And that particular
biopsy may not show as much, but there might be
other areas where there's very high amounts of
dystrophin produced, and that's where the
beneficial effects would be occurring.

That's just my opinion and from what I've
read.

DR. ALEXANDER: Thank you. Just a comment
that I'll make -- Caleb Alexander -- is just
the -- I'm surprised that there's not more
consensus. I accept that there may not be, but
it's surprising to me that there's not more
consensus, scientific consensus, regarding what
would constitute clinically meaningful levels of
dystrophin.

I will say that I think that the sponsor
question, the adequacy of Western blot data,
arguing that it really can't be compared with
published reports, but also made the case that in prior reports of BMD, Beckers, that dystrophin levels are between 2 and 100 percent.

The fact that there were also -- it sounds as if early in the clinical development program, there were estimates that dystrophin levels may have increased as much as 20 to 50 percent, which I think we would all argue or believe or feel would be incredible results relative to, for example, what we're seeing here.

Now, I'm referring to the actual quantification with Western blot, and that clearly was a pivotal event that appears to have had a very profound impact on the subsequent decisions that the sponsor and the FDA reached regarding the next steps in the development program.

Dr. Romitti?

DR. ROMITTI: Yes. Paul Romitti. So in looking at this and thinking about laboratory methods in general, I think they're constantly evolving. We are what we are today and we have the best methods available.
While we may not know enough as we wish we would with regard to dystrophin levels, I think that after the instruction by the FDA to have three blinded reviewers, I felt more confident with those results, study sample aside, than I did with just one reviewer, which I think is not quality science. So I think even though the amount may have been less and it may have been less striking than originally reported by that one reviewer, I still think that there is evidence here that there is a difference. And the evidence may not be high, but I think back to many studies that I'm involved with, which are other studies where we're trying to study biomarkers of exposure, they're challenging.

As the laboratory methods get better, we get better at doing it. We can do it better in animals than we can in humans. But we get better and we get better in humans.

So I think given the state of the science today, I think that there is enough evidence here to say that with the re-analysis and the rereads, that we do see some difference in dystrophin.
(Applause.)

DR. ALEXANDER: Dr. Dunn and then Dr. Onyike, and then we may move onto the next question, keeping in mind that we have seven, and we're projected to be about 45 minutes to an hour over at this point.

DR. DUNN: Billy Dunn, FDA. You mentioned the difference. I just want to make sure I fully explore that so we understand. When you mention the difference, that obviously implies difference in A and B. Can you just talk a little bit more about what specifically you find the difference between?

DR. ROMITTI: I'm referring to the difference in the tables that were shown that showed the single reviewer versus the three blinded reviewers, and there was still a difference, if I recall, of 17. There was a still a total of 17 overall as opposed to --

DR. DUNN: Right. I'm sorry. I didn't actually mean the data in presentation as much as the change from what dystrophin,
where -- obviously, you're referring to the 0.9 that was observed. And I think what I really want to try and understand is what change, do you think, that represented, what the comparison is.

DR. ROMITTI: From the data that we have been given, the comparison is around 0.08, is what I recall the comparison is.

DR. ALEXANDER: Can we see the table, please? I wonder if that would be helpful in clarifying this point.

DR. BASTINGS: Yeah. If you can pull Slide 37 of FDA presentation?

DR. ALEXANDER: Dr. Nuckolls, do you want to first try -- I'm sorry. Dr. Romitti, do you want to try to address? I think the question was --

DR. ROMITTI: Okay.

DR. ALEXANDER: What I understood you saying was that you have more confidence in the three blinded reviewers than just one reviewer, and so the amount --

DR. ROMITTI: So there are two different measures here of dystrophin. There's the positive
fibers and then we have the PCR -- the Western blot, excuse me. So I'm lumping both into my discussion. If you would like me to reserve my discussion for one, that's fine.

So this is what I'm meaning here for one and the other is the 0.9 versus the 0.08 with the, what I'll call FDA-accepted method of analysis being the Western blot.

DR. ALEXANDER: Okay. Can you try one more time, please? Just to be sure we have it straight on the record, just making the point again.

DR. ROMITTI: Okay. I'm taking a look at both measures that were used. The sponsor's original endpoint was positive fibers. And I'm looking at this, and I'm saying I was uncomfortable with the original analysis given it lacks replication. I was more comfortable that there appears to be some kind of change here with the re-analysis by the blinded reviewers for this approach.

But I'm also commenting on the FDA's suggestion of using Western blot as well to
quantify dystrophin. And with that and with the unknown threshold, if there is one, for what is enough dystrophin to see change, I think both provide evidence there has been some change.

DR. ALEXANDER: Okay. Thank you very much. Dr. Onyike?

DR. ONYIKE: Yes. I was just intrigued earlier by the commentary. I think it was from a gentleman who is my line of sight about how dystrophin effect might transfer beyond specific fibrils to their neighbors. But I don't fully understand how this might work. So perhaps you might elaborate.

DR. ALEXANDER: Who is the question for?

DR. ONYIKE: Well, it was a professor in the audience who had talked earlier about evidence that fibrils might generalize -- I mean, sorry, that dystrophin levels --

DR. ALEXANDER: I'd like to --

DR. ONYIKE: Well, if you can't do it, that's fine.

DR. ALEXANDER: Yes, yes. I --
DR. ONYIKE: I was intrigued by --

DR. ALEXANDER: Sure. Thank you. I mean for the record, I'd like to have the question be known, but I think in the interest of being sure that we give due consideration to the remaining questions, we should move on, unless Dr. Ovbiagele has a final comment on this?

DR. OVBIAGELE: No. I just wanted to say, it's one thing to talk about change, but the other thing is I think be asked about the clinical correlation. So whether there's change or not is one issue.

But if you remember, if you looked up the four individuals with the best 6-minute walking times, there was actually no correlation. Two of them had the highest levels of dystrophin and two has the lowest levels of dystrophin.

So to answer that question, the clinical meaning is not clear based on that.

DR. ALEXANDER: Okay. Thank you very much. So my job is to try to summarize what I've heard, and this included the following. There's moderate
evidence for production of dystrophin, though we
don't have a clue how much is clinically
significant, also hard to know if what is produced
is as clinically active as natively produced normal
dystrophin. There might not be a threshold effect
or the threshold may vary wildly among individuals
with no idea what the range is, but it may dip very
low.

The conclusion about whether or not there's
a large amount produced depends upon the methods
used to assess this, not convinced that the
biopsies were correct biopsies or not; dismayed at
the quality of some of the comparative evidence;
plenty of evidence to support mechanism of action.

The big challenge is that there's not enough
pre- and post-treatment comparisons on the same
patients, and this is what question 1A is focused
on. Comparisons were with other patients.

The issue was to produce dystrophin, and the
drug did do this. Believe that we are seeing clear
benefit and that the amount produced is sufficient
to account for the clinical benefit observed;
whereas, the dose effect, maybe not enough of a range examined in doses, and that might account for the absence of a dose response.

The biopsy represents a very small part of the musculature and may not show you as much. There may be other areas where there are very high amounts of dystrophin produced.

Surprising that we're not further along in figuring out what amount of dystrophin would constitute a clinically meaningful response and also surprised that there's so little consensus about this.

More confidence in the 3 blinded reviewers than just one reviewer. Although the amount made may have been less and less striking than initially reported by the single reviewer, there's still evidence that there is a difference. And this was referring to both the immunofluorescence, as well as the Western blot.

Belief that there's a change in the reanalyzed data over time, but comparing that with the Western blot data provided is difficult. And
we are asked about the clinical correlation, as well as change, and we're asked to evaluate not only the change in dystrophin levels but also the clinical correlation. And the final point that I heard was that there was no obvious correlation between the dystrophin levels and the change in the 6-minute walk test.

So Dr. Woodcock?

DR. WOODCOCK: Yes. When you move to the next question, I'd like to have a conversation with the committee about what you're voting on, so you're clear about what you're voting on, question 2, in this part of the discussion.

DR. ALEXANDER: Thank you. We'll be sure to do that.

So for voting questions, we'll first be discussing the questions, subsequently voting on it, but I'll read now for you about the voting process.

For voting questions, we'll 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 the 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 designated federal officer 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're also requested to please state a very brief 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.

So the voting question that we're posed with is, has the applicant provided substantial evidence from adequate and well-controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical
benefit?

Dr. Woodcock?

DR. WOODCOCK: Yes. This is the standard for accelerated approval. So this would be a vote on whether or not that surrogate endpoint of dystrophin is reasonably likely to predict clinical benefit.

So this is a question about approvability, and my point is that you have to factor in the clinical data in this discussion, what weight you think it gives to the reasonably likely decision. So you're talking about, first, whether question 1A, which you already discussed, whether or not dystrophin was increased.

Now, reasonably likely, as you've already discussed and I've mentioned in my opening remarks, there is no standard established. And for this condition, there is no threshold established because there's never been a drug to do this.

So people don't know. They've looked at natural experiments such as Becker's, and you see that there is a range of response as was said
earlier. So the question that you're being posed, if you follow me, is does the clinical experience in these trials, with these patients, lead you to believe, if you believe dystrophin was increased, that that increase is reasonably likely to predict a clinical benefit?

Do you follow me? Okay.

DR. ALEXANDER: Are there clarifying questions for Dr. Woodcock or other members of the FDA regarding the question?

(No response.)

Okay. If not, then we'll vote now. So once again, the question is, has the applicant provided substantial evidence from adequate and well-controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?

(Vote taken.)

DR. ALEXANDER: Please vote again in case you haven't. Although your vote only counts once.

DR. CHOI: Everyone has voted. The vote is now complete.
DR. ALEXANDER: Thank you.

DR. CHOI: For the record, we have 5 yes, 8 no, zero abstentions.

DR. ALEXANDER: So we'll now go around and briefly state our name and vote into the record, as well as a brief rationale for why you voted as you did. So we'll begin with the first voting member on this side.

DR. HOFFMAN: Richard Hoffman. I voted yes because of all the reasons I mentioned earlier.

DR. ALEXANDER: Can you briefly state those very succinctly?

DR. HOFFMAN: By all the testing methods that were used, PCR, Western blot, immunofluorescence, I believe that there is proof that dystrophin was produced and that eteplirsen was responsible for it.

DR. ALEXANDER: Thank you. Please proceed around the room.

DR. GREEN: Okay. Mark Green. I voted yes. I believe that dystrophin is made by the drug. As I said before, I'm very troubled by not
understanding a clinically significant amount. And I'm not sure at what level I'm supposed to say this, but I've been extraordinarily influenced and impressed by the people who spoke about this drug earlier and their observations.

(Applause.)

MR. DUPREE: To me --

DR. ALEXANDER: State your name please.

MR. DUPREE: Benjamin Dupree. Do I state what my vote was? I voted yes, and the reason behind that is that it appears to me, as has been described by Paul Romitti, that there's a change. And I think given the clinical results that were described, it's reasonably likely to predict clinical benefit.

DR. ALEXANDER: Please just continue around the room.

MS. GUNVALSON: I'm Cheri Gunvalson, and I voted yes. I believe the dystrophin was produced, and that was what the goal was. And I believe it's demonstrated in the clinical abilities of these boys, that you don't regain lost milestones in
Duchenne, never.

(Applause.)

MS. GUNVALSON: And I think that the qualitative data was good, and I would hope that the FDA would require qualitative data on future studies, because as a public health nurse who does studies on populations, we look at quantified data and quality data. And in the trends in the quality data, you can almost find out more. So number of falls I think is tremendous information on how a drug is working.

DR. ALEXANDER: Thank you. Dr. Kryscio?

DR. KRYSCIO: Richard Kryscio. I voted no. I guess I'm the first no vote. I voted no because I don't think the studies were well controlled. I was concerned with using different tissue samples. I was concerned about a lack of correlation that people who have little or no -- people who had substantial problems clinically may or may not have had a lot of the dystrophin actually produced. Perhaps it's a measurement issue, but that's the reason I voted no.
DR. ROMITTI: Paul Romitti. And I hit the
wrong button. I apologize.

(Applause.)

DR. ALEXANDER: I'm sorry. Please hold your
comments. Dr. Romitti?

DR. ROMITTI: Yes. I'm sorry. I must have
hit in between, so I apologize for the -- if I
can't change my vote, I understand.

DR. ALEXANDER: But just please, state for
the record what you intended to vote and your
rationale.

DR. ROMITTI: It's what I said before. I
think we do see some difference. Would I have
liked a better controlled study? Yes, but we do
see some difference. There was some evidence of
improvement in endpoints given the overall size of
the study.

DR. ALEXANDER: So for the record, your vote
is a yes?

DR. ROMITTI: Yes.

DR. ALEXANDER: Thank you.

(Applause.)
Dr. Nuckolls?

DR. NUCKOLLS: Glen Nuckolls. I voted no. I think that Western blot comparison is the most important for determining dystrophin level. And the samples were done with samples from different patients in different muscles. And I don't find that this fits the definition of an adequate and well-controlled study.

DR. FOLEY: Reghan Foley. And I voted yes. I believe that Western blot in combination with immunofluorescence are very important, and that RT-PCR proves that drug was working by its intended mechanism. And there's likely patchy dystrophin expression, but I think the clinical efficacy seen is likely secondary to that increase in dystrophin expression no matter what degree increase was seen.

DR. KESSELHEIM: My name is Aaron Kesselheim. I voted no. I wrote this question down into four parts. There was the applicant-provided part, the adequate and well-controlled studies part, the induces production part, and then the reasonably likely
part.

For me, I felt like the induces production part was the easiest. It clearly does seem, to me, to induce production. I felt like the studies that were provided by the applicant were not adequate and well controlled because of the problems that I discussed earlier in terms of the sampling, and the comparisons that were made, and the lack of adequate comparators before and after, and the staining issues that we went over before.

Then the final part is the question of whether it was reasonably likely to predict clinical benefit. I was moved a lot by the lack of association between the findings from the results in some of the clinical findings.

I think it is still an open question though, and I think that it is possible that the drug does work, but that the methods being used to test for the drug, in this case, just weren't specific enough to identify that.

DR. ALEXANDER: Caleb Alexander. I voted no, and I had concerns about the techniques whereby
dystrophin was measured, the relatively modest or
very modest absolute amounts of dystrophin
produced, as well as the absence of more
scientifically rigorous selection and management of
controls to allow for, what I felt, would be
comparisons that would lead me to be more
confident.

DR. ONYIKE: Chiadi Onyike. I voted no. I
voted no because even granted -- and would be
willing to accept -- even if one is willing to
accept, and I am willing to accept -- for the
purposes of this question anyway -- that eteplirsen
led to some dystrophin production, but it's very
small. And it's still within the range of what
people with the disease have.

So with that in mind, it's very important to
have some sort of coupling between the dystrophin
production and the clinical effect. We don't have
that. So I can't get from dystrophin production,
even if I accept it, to any kind of clinical effect
without some understanding of a threshold or the
mechanisms -- if it were large amount, we would
have a different conversation but it's a very small amount, too small to just go from dystrophin production to clinical effect.

Now, as to whether there was clinical efficacy, I think that's a separate issue in terms of the clinical measures. I think it's a separate question.

I do believe it is possible, for example, for a medication to have an effect without you knowing why. We have Tylenol, for example. We have heparin. We don't know how they work. It doesn't mean that we should throw them out.

So I'm not entirely sure that one should lock the clinical effect to the dystrophin production.

DR. ALEXANDER: Thank you.

DR. GONZALES: Nicole Gonzales. I voted no. While I believe it is more likely than not that the drug does produce dystrophin, the clinical data, as presented with the use of historical control, was very problematic for me and does not convince me that whatever dystrophin is being produced is
demonstrated in a clear benefit clinically.

DR. OVBIAGELE: Bruce Ovbiagele. I voted no
for many of the same reasons that have been
mentioned. I had problems with the techniques.
But even if I give a pass to the techniques and
there was some dystrophin production, I don't think
the study was well controlled. And most
importantly to the question that was asked, whether
the level was likely to produce a clinical benefit,
there was a lack of correlation between dystrophin
levels and the outcome. So that was a no for me.

DR. ALEXANDER: Thank you. So I'll briefly
summarize this for the record. Some of the votes
in favor were influenced by the reports of
individuals that provided comments during the open
public hearing. There was a comment that a change
of levels is present. This was felt to be
reasonably likely to predict clinical benefit.

There was a comment that dystrophin was
produced, and that was the goal and demonstrated in
the clinical abilities of boys, and you don't
regain lost milestones otherwise; support based on
the qualitative data that was provided, number of falls.

Those voting no did so in part because of concerns about the studies not being well controlled, using different tissue samples, lack of correlation between clinical progress and changes in dystrophin produced, perhaps a measurement issue.

There was a comment that one does see some difference, some evidence of improvement in endpoints based on the size of the population. Western blot comparisons are most important, were felt to be most important by a panelist. Samples were done from different patients with different muscles and doesn't fit the definition of adequate and well-controlled study.

PCR suggested the drug is working by intended mechanism, so a belief that the clinical efficacy was likely due to differences in dystrophin seen. Another panelist pointed that there was evidence of induction, or production, I should say, but the studies, once again, that were
provided by the applicant were not felt to be adequate and well controlled.

With respect to whether or not these were likely to be -- the dystrophin change was reasonably likely to be predict clinically benefit, the panelist was moved by the associations presented but thinks it's an open question, possible that it works, but the methods need to test for this weren't specific enough, and so that panelist voted no.

Concern about the quality of dystrophin production data, about the techniques that were used and the absence of more rigorous controls, very small amounts of dystrophin and the range of what people with the disease have untreated, important to have some coupling between dystrophin production and clinical effect.

Even if one accepts the dystrophin production, hard to get from there to clinical effect. If it was a very large amount of production, we'd be having a different conversation.
Another panelist, once again, more likely than not that the drug produces dystrophin but the clinical data are very problematic and not convinced that the dystrophin that's produced is generating the benefit that we see. And the final panelist commenting problems with techniques, and even if this is accepted, here again, the study wasn't well controlled. And even if so, lack of correlation between levels and outcomes.

With this, we'll move on to question number 3, which is a discussion question. Discuss the strengths and weaknesses of the clinical evidence of efficacy provided by study 201/202 with particular consideration of the design of the study, sample size, statistical methods, general concerns regarding comparison to a historical control group, specific concerns with respect to comparability of these two groups; in particular, how motivational factors and differences in assessment of physical performance outcomes may have affected the 6-minute walk endpoint and other endpoints, and any other issues
that you think may be important.

So we have a few moments for discussion here. Once again, please keep your comments or questions very crisp and focused on this question at hand.

Ms. Gunvalson?

MS. GUNVALSON: I've seen a lot of 6-minute walk tests, and I can honestly say that these boys know what's going on. They know they're being timed. They know this is a deadly disease. They're on the internet. I can honestly say I've not seen a boy motivated to do his best, and so that's my opinion.

As far as -- yes, I just don't -- I know what coaching is about. I have kids and athletes, but you can't coach these kids to walk faster. They have this waddle gait that if you push them to go faster, they fall. It's just not possible. I mean, it's like a balance beam how they do it, and they go to the best of their ability.

DR. ALEXANDER: Thank you. Dr. Green?

DR. GREEN: Well, I think we all agree that
placebo controls are often flawed, but historical controls are worse. And that was so well pointed out in Dr. Temple's discussion on historical controls.

So the data, my yes vote had to do with external influences that I believe were significant. But the way the study is designed, it gives me very little comfort.

DR. ALEXANDER: Thank you. And I'll just make a comment. Caleb Alexander. One contrast that I wanted to underscore that I noted was the difference and the conclusions that one reaches when one looks at individual trajectory level as a function of age at enrollment. And we saw several analyses, I think three analyses, for the historical controls and then three for the synergy data by the FDA that provided this type of analysis that are following individual patients over time as a function of their age at study enrollment.

I did note that the sponsor had at least one slide that had information that wasn't just means or averages but actually allowed for individual
level trajectories, although even this slide only
looked at the 6-minute walk test as a function of
length of treatment, not patient age.

So I just wonder whether there's
information -- and so that seems, to me, to be a
really important set of slides and ones that point
in a different direction than if one looks at plots
of the primary outcome as a function of study
enrollment alone.

Dr. Gonzales?

DR. GONZALES: Nicole Gonzales. I just had
a comment. Just reading the data from Sarepta,
every single secondary clinical endpoint seemed to
be so positive. And listening to the testimonials
and the experiences of the boys and the families,
it just seems to me that had there been a true
placebo group, that the differences would have been
so striking and that the study may have even been
stopped soon. I'm trying to understand why there
wasn't an adequately powered placebo group.

DR. GORDON: Someone else has their mic on.

DR. ALEXANDER: Just one minute, please.
Does the sponsor want to respond to a particular question about the absence of a placebo group?

DR. KAYE: Yes, just to be able to address to that about the placebo. So I think just to be clear, I think when we had initially done the phase 2 study, there wasn't enough drug at that time. We didn't have the ability to manufacture until almost two years later. So this was designed as a phase 2B.

When we had enough drug to actually do a placebo-controlled trial, because of the response to the fact that this drug produced dystrophin and also the clinical response, there really wasn't a possibility at that time to be able to really do a formal placebo-controlled trial.

This was exactly the same problem I had with my Myozyme that you heard about earlier from Dr. Temple. We had to make a decision at that time what was the in the best interest of patients, and we decided to do the external control, which is the next best thing.
If I can have the slide up, one of the things that we did -- and I agree --

DR. ALEXANDER: I'd like to move on, actually. Thank you.

DR. GORDON: Okay.

DR. ALEXANDER: Thank you very much.

Dr. Onyike?

(Audience groans.)

DR. ONYIKE: I think when we have what I perceive as a weakness on the biological plausibility front and you have a small sample and a control group that is not optimal, and when you look at the effect of age corrections on the outcome, the 6-minute walk test, you do want some validity.

But when you turn to the 10-minute walk/run results, or to the sit/stand, and to all the other things that should provide convergent validity regarding the outcome, what you find is that you don't find any positive results.

So across the board, if a drug is effective, given its pharmacologic effect, it should have
effect on multiple outcomes, not just the single one. And that isn't happening in this data, so that's my one problem I have.

Now, in terms of the testimony from the families, what really struck me is that a lot of the testimonies were about -- there was a picture. I think it was Austin who is stacking cans, and that's upper limb strength. And you look at -- all the outcomes in this study were about limbs, about the limbs or the trunk. And there is no study outcome that's about upper limb strength or grip, and I think that is a very unfortunate thing about outcomes assessment in this field in general.

You want something that's tangible to quality of life. You want something else that accounts for the distribution of effects across the various muscles, and without upper limb testing, you don't have that.

DR. ALEXANDER: Can I just ask for you to clarify the first comment that you made? What I understood you to say is that you have concerns about biologic plausibility because the drug isn't
having an effect on multiple outcomes. But can you specify what you mean by that?

DR. ONYIKE: Let me clarify. When I'm talking about plausibility, I'm going back to the dystrophin. If the dystrophin data is not decisive and you have a clinical outcome that arises from comparisons with a suboptimal control and that wilts under age correction, you need all the other outcomes to line up in the same direction for the single outcome to be considered a valid measure of efficacy.

Now, it turns out that none of the other outcomes, as depicted in the FDA analysis, lined up with a positive effect.

Now, when you listen to the testimony from the families, one of the things that was highlighted is opening cans, opening packages, lifting things, and none of that is captured by the NSAA, or the 6-minute walk test, or the 10-minute walk test.

So you have an unfortunate discrepancy between what the families are describing as
tangible benefits and what is actually measured. We're not even talking about negative measurements now. We're talking about non-measurement of areas of function that might have delivered some clarity about the effects of this drug.

DR. ALEXANDER: Okay. So you're questioning the biological plausibility and making the point that one doesn't have a lot of dystrophin production, and then reporting that, in that case, that one would want all of the outcomes to line up.

But does the sponsor not present a case for the outcomes being consistently positive? By what basis are you deciding or the claiming that the outcomes don't line up?

DR. ONYIKE: So when you look at slides 92 through 94, and when you look at 87, 88 --

DR. ALEXANDER: Can we see one or two of these just to help us, remind us what this covers?

DR. ONYIKE: So 87, if we can look at 87, it covers both the NSAA and the 6-minute walk test. Slide 88 covers the rise time. And all of these do not show a difference between the groups when
plotted as a function of age of the subjects.

So basically, outcome after outcome after outcome is lining up as no effect, when age-corrected. So there's no validity to the -- you can't anchor claims of benefit on one outcome when the rest of them are not falling in line, particularly when your biological plausibility and your control groups are subject to question.

DR. ALEXANDER: Okay.

DR. ONYIKE: But I feel that there's an inadequate measurement of treatment effect to begin with because there's no measurement of upper limb strength.

DR. ALEXANDER: Okay. Thank you. This is Caleb Alexander. If you can leave the slide for a minute, I'd like to give the sponsor a chance, because this is the second time that this type of analysis has been raised during this question discussion.

So the question for the sponsor is whether or not you considered or if you could help the
panel interpret the data that's presented here or in slide 66, which precedes it, I believe. But these all show a similar analysis of individuals over time stratified by age. And the request is just to help us interpret -- provide for us your interpretation of what these data represent.

DR. KAYE: So if we just look at the rise time -- and Dr. McDonald had described it -- what was recorded is when it was really the ability to rise. So those boys with the higher rise times had with support. So that wasn't what we did in the analysis; it was just the ability to rise. And they were all less than 75 seconds.

If I could have a slide up --

DR. ALEXANDER: I'm sorry. Just --

DR. KAYE: Oh.

DR. ALEXANDER: This is another example of that, if you could provide -- sort of help us understand how these types of analyses complement those that look at the effect over time rather individuals plotted out over the course of -- based on age.
DR. KAYE: Sure. Well, I really think the main difference, though, is we're also looking at the time on treatment. So if we were looking at two external control groups and trying to see what the difference was, then I think the age. What we try to do is match up the baseline ages, 6-minute walk test, all of the other parameters, the steroid use, and then look at what is the time on therapy.

What this doesn't really show is what is the ability -- what's the change we see in response to the treatment. And I think when we look at that, that's where we're able to see the treatment benefit.

I think getting back to the question as far as what do we see as far as other things, we did do grip strength, both left and right, for 4 years, and we did not see any decrease in that. That was one of the exploratory measurements that we used.

We also looked at pulmonary function over 4 years, and as you heard, that's an important event. And the pulmonary function should go down anywhere from 5 to 8 percent per year. Every study
that's ever been done, that's with or without steroids.

This study showed 2.5 percent per year. And again, if we look that cumulative data and looking at all of the information about -- looking at the number of boys -- slide up please -- again, looking at the treatment difference, if we look at this in regards to what we see, we always see it in benefit of treatment.

So 6-minute walk test, you heard about. Loss of ambulation, it's even more. There was a difference, but it was always in favor of eteplirsen or the North Star and the ability to rise, and then also what I just mentioned was the pulmonary function.

So if we look at it from that perspective -- and I think it is important not to just look at the difference of ages because you can't judge the boy at an age, what you've heard from Dr. McDonald. It's how long are they walking, what is their ability to rise, all of those factors, how much steroids were they on.
So I think it's not a fair comparison to just look at the age because a boy at age 11 who's walking 600 meters is very different from a boy at age 11. So what we try to do is make this comparison at baseline when we started the treatment. That's how every study is always done because you have to look at what's the time on drug. And I think when you do that, it's always in favor of eteplirsen. And I think that's the important thing that has to be done.

We appreciate the small size of the study, but I think if you look at the totality of the data, including the upper extremity function, it's always in favor of eteplirsen.

DR. ALEXANDER: Thank you very much.

Dr. Gordon, did you have comment? And then I think we'll just have one more, and we'll move on.

DR. GORDON: The sponsor wanted to make an additional comment.

DR. ALEXANDER: Can you speak into the microphone? I'm sorry. Your comment?
DR. GORDON: Sure. The sponsor had asked me to make a comment.

DR. ALEXANDER: I see. Dr. Bastings and then Dr. Kesselheim.

DR. BASTINGS: Yes, I think I heard Dr. Kaye make a comment that the kids were helped when they were attempting to rise. You mentioned that there was some help provided. I would like him to expand on that a little bit.

DR. KAYE: Yes. So when we looked at the rise time, I think one of the things that obviously we wanted to make sure is that we did it exactly the same way. So when the rise time was done, it was the ability to rise independently, because if you're hanging on to a chair or if you're hanging on to the wall and you're getting up, it will take a longer period of time.

So we specifically wanted to make sure that we did the rise time from the external control to our eteplirsen-treated boys in exactly the way. So when you look at that -- and again, all of these boys who got up did it in less than 25 seconds;
they all did it unaided. And then when you do that
exact comparison, then it's over half of the boys,
55 percent, were able to do that unaided compared
to 12 percent.

What was shown in that graph is the boys
from the external control who had lost the ability,
their rise time wasn't included, so it was just the
boys who -- so we actually tried to measure the
boys who could walk unaided, so it was a
difference.

I think that's really the focus, is that
what is the difference. When you do an apples-to-
apples comparison, you do see a difference.

DR. ALEXANDER: Okay. So just to clarify,
were the boys -- do the rise times uniformly
reflect unaided rise times or is some of them
aided --

DR. KAYE: Yes, that's correct. All of them
that are unaided that are used in this analysis.

DR. ALEXANDER: So does that answer your
question, Dr. Bastings?

DR. BASTINGS: Yes. So you're referring to
the rise time that were shown on slide 88 of the FDA presentation?

DR. KAYE: That's correct.

DR. BASTINGS: Like when we have 40-, 45-second rise times, there was no help provided?

DR. KAYE: No, no. Those 45-second rise times, they were using external support. That's the difference. So in other words, when we looked at the boys, what we looked at here is could they walk unaided, and that wasn't recorded for the boys in the external control. And maybe Dr. McDonald can just explain it.

DR. BASTINGS: I don't think this information was provided in the NDA.

DR. ALEXANDER: Okay.

DR. McDONALD: Could I just clarify this data? This data is based on the North Star subscore of whether you can perform the rise ability independently or in an impaired fashion, or if you cannot perform it independently; you've lost the function.

So at 3 years, 55 percent of eteplirsen
treated patients have continued independent ability
to perform the rise ability, whereas only 8 percent
of the external controls.

Now, we made the point that as a prognostic
endpoint, it's really the loss of rise ability;
its not how long it takes you to do the rise test.
It doesn't matter whether you're zero to 5 seconds,
5 to 10 seconds, or even greater than 10 seconds;
that's not prognostic for loss of ambulation. It's
the loss of rise ability, which this data captures
based on the North Star subscore of independent
rise time.

DR. ALEXANDER: Okay. Thank you very much.

I'll try to summarize what I've heard
regarding question number 3. There was a
comment -- and the record will reflect a more
accurate capture of everything because there was a
fair amount that was discussed.

But there was a comment regarding boys
knowing what's going on, a comment regarding
cconcerns about placebo controls often being flawed,
cconcern with regarding historical controls often
even being more flawed as represented by or demonstrated by Dr. Temple's presentation.

There was a comment regarding the fact that every secondary clinical endpoint seemed so positive and listening to the experience of boys and their families so positive. And if there had been a placebo group, the panelist felt that the study would have been stopped, yet they queried why a placebo wasn't done.

The answer provided was that there wasn't enough study drug available, and then at the point when there was enough available, it wasn't possible because of conclusions that had been reached regarding the assays on dystrophin at the time.

There was a comment regarding the results not being biologically plausible because we don't have a lot of dystrophin. And especially in that setting, one would want all of the other outcomes to line up with very clear evidence of efficacy, and that one doesn't have this, based on the FDA's analyses such as in slides 87, 92-94, all of which raise concerns or failed to show a
significant -- I'm saying not statistically
significant but rather failed to show a large or
observable qualitatively significant difference
between the groups.

The family testimony includes outcomes that
were not captured by the measures assessed, and
this was felt to be unfortunate and an unfortunate
discrepancy between what families were reporting
and what was actually measured.

There was encouragement to -- the sponsor
was queried regarding the analyses, but that the
FDA provides examined patients over time stratified
by the age at which they started treatment or
entered the historical control, and the sponsor
felt that these analyses don't show the change that
we see in the response-to-treatment; that one can't
just look at the patient age but has to look at the
time on therapy.

The sponsor also commented that pulmonary
function should go down 5 to 8 percent a year, but
didn't. I presume I was understanding correctly.
And the same with grip strength, and that these do
support the variety of additional outcomes that were assessed.

The sponsor provided their analyses suggesting that NSAA, the North Star assessment, and ability to rise, and 6-minute walk test, all in favor of the study drug based on their analyses, and that kids were helped.

Then there's some uncertainty, a little bit of unclarity on my part regarding whether or not assistance was provided to kids and what constitutes assistance, whether this was mechanical devices or human help and the like, but that can be clarified. And I'll just note that ambiguity in my mind for the record.

With that said, we'll move to question 4, which is a voting question. Were decisions to administer the 6-minute walk test versus conclusions that the patient could no longer walk sufficiently objective and free of bias and subjective decision-making by patients, their caregivers, and/or healthcare professionals to allow for a valid comparison between study patients
in studies 201/202 and an external control group?

So we'll move to voting on that now.

Once voting is concluded, we'll begin again
with -- well, why don't we begin at this side of
the table this time, to my left, once voting is
concluded. And just for the sake of time, rather
than my calling on you, please just state your name
into the record and your vote, and a brief
rationale after the person immediately to your left
has provided their information.

DR. HOFFMAN: [Inaudible – off mic.]

DR. ALEXANDER: Yes, C is -- I'm sorry.
D is abstain. So yes is B, like boy; no is C, like
Charlie; and D, like dog is abstain.

DR. HOFFMAN: [Inaudible – off mic.]

DR. ALEXANDER: So let me just read the
question just to be clear. The voting question is,
were decisions to administer the 6-minute walk test
versus conclusions that the patient could no longer
walk sufficiently objective and free of bias and
subjective decision-making by patients, their
caregivers, and/or healthcare professionals to
allow for a valid comparison between patients in studies 201/202 and an external control group?

So if you believe that the decisions were sufficiently objective and free of bias and subjective decision-making, you would vote yes. And if you believe they were not sufficiently objective and free of bias and subjective decision-making, you would vote no.

(Vote taken.)

DR. ALEXANDER: Please enter your vote one final time. Press the button firmly.

DR. CHOI: Everyone has voted. The vote is now complete. For the record, we have 5 yes, 7 no, 1 abstention.

DR. ALEXANDER: So we'll begin with Dr. Ovbiagele.

DR. OVBIAGELE: Bruce Ovbiagele. I voted no. I'll just be quick. Two reasons. Number 1, of course, it was open label. I would have loved to see a blinded adjudication of the outcome. That would have at least helped a little bit.

Then, the other issue was in the control
groups themselves, it seemed as if in some situations, patients were deemed unable to do the 6-minute walk test, which was not necessarily appropriate in some situations. So I didn't think it was necessarily objective.

DR. ALEXANDER: I'm sorry. Can you repeat the second point? The first you made was about open label and blinded adjudication. But what was the second point?

DR. OVBIAGELE: The second point was about in some situations, for the control patients, they were deemed not able to do the 6-minute walk test. And in those cases, it might not have been appropriate for them to have been deemed unable to do that.

DR. GONZALES: Nicole Gonzales. I voted no. For me, this has nothing to do with motivation. I think it's crystal clear to me that boys are extremely motivated to walk. And for me, this has to do with the difficulties with using a historical control, as has been demonstrated, not just in the neurology but in all of medicine and all of the
biases that we cannot measure.

DR. ONYIKE: Chiadi Onyike. I voted yes. I believe that what -- even though it's true that one can't say that it was very systematic with respect to looking at the study versus looking external controls or that you can argue uniformity and ascertainment of the scores, I don't think that the magnitude of error would be enough to have distorted the study outcomes if it were not for the small sample size and other key problems.

DR. ALEXANDER: Caleb Alexander. I voted no. I had concerns primarily about the -- well, concerns both about the potential ways that the controls may not have been exchangeable, comparable with the treated patients, and these can be very subtle.

Really, the impact of this is unknowable at this point, so it's not so much that I'm convinced that they're different as that it's unknowable, the magnitude of difference that may have been present. So that was my primary concern.

DR. KESSELHEIM: Aaron Kesselheim. I
abstained. With all due respect, I didn't think
this was a very good question, the way it was
written, and I had trouble interpreting it in order
to make a firm yes or no answer.

I felt like I was convinced through the
course of the day today that the 6-minute walk
test, though it is a subjective measure, it could
be a valid intermediate endpoint. But I had
trouble with the context in which it was used and
the results that came up in regard to the
historical control. I felt like it was more
appropriate to address that in the seventh question
as opposed to this question.

So because I couldn't exactly -- because I
agree with part of the question but not another
part of the question, I chose to abstain.

DR. FOLEY: Reghan Foley. I voted no due to
the problems with historic controls and seeing that
there were patients for whom there had been times
were at 10-meter walk or run but no time for the
6-minute walk.

I just think that the most important issue,
really, is the preserved ambulation and ability to
rise, which is kind of, to me, incontrovertible
evidence. But with this data with historic
controls, it was hard to control for other sites
and historically.

DR. NUCKOLLS: Glen Nuckolls. I voted no.
The predetermined selection criteria for the
control group were not sufficient to control for
biases. And since it's an open label, and I also
agree with your point about subjects that had a
12-second, 10-meter walk but were listed as
non-ambulatory, these caused me to question the
objectivity and comparability of a 6-minute walk
test.

DR. ROMITTI: Paul Romitti. I wavered
between yes and abstain. Just for the record, I
did push the correct button this time. Reason
is -- a couple of reasons, one, a fellow panel
member talked about upper body strength, but I
heard testimonies from more than one child who said
they were still walking after being on the drug.
So there was also measures of lower strengths, so I
do think there was consistency there.

The biggest problem I have with this -- and I took the question literally, which is why I gave it a yes. After working for a decade with a 30-year cohort of patients with Duchenne and Becker muscular dystrophy, I believe these patients will do anything they can to maintain their mobility, and I don't think there are any extra motivated to do so.

I think the other thing is, is I think we're just losing a bit of grasp here on the heterogeneity of this condition. And so in analyzing data by age of the subject I think is inappropriate.

I think it's more appropriate to look at disease progression. After seeing after symptom onset can happen at 2 years for some and 5 years for others, I don't think that's the way to go. So I was not convinced by the evidence that the FDA presented by year, and I think it's more appropriate to go by the stage of development where the child is.
DR. KRYSCIO: Richard Kryscio. I voted no. I was disappointed that the data was not analyzed; the way the subjects were randomized, its delay-start designed. They introduced historical controls; I'm not convinced that they are necessarily comparable. They had problems, as were mentioned, throughout the day.

My real problem is the endpoint itself. I mean, it just looks at the lower body; it doesn't look at the upper body. And we've heard many comments about upper body strength versus lower body strength.

There are a lot of better measures. There are diseases where you have more of a functional rating scale. Take a look at ALS, which has similar problems with people losing ambulatory status. They have well-designed trials with lots and lots of patients with a well-accepted endpoint.

This is not a good primary endpoint where you have a floor effect when people can't walk, and statistically, it just doesn't make sense to try to average those numbers in the plots. Those are
called spaghetti plots in the statistical
literature.

MS. GUNVALSON: I'm Cheri Gunvalson, and I
voted yes. I believe that there was a
differential, and it has also demonstrated in the
boys that showed us upper body and lower body
increases.

I think the FDA should require a
non-ambulatory arm in every Duchenne trial because
there are a lot of things that need to be studied.
If a drug is approved, and non-ambulatory boys who
are on a cohort of cardiac meds and things like
that, that should be looked at in a trial setting
for safety, not after a drug is approved. And
also, there are things you can measure but safety
is a main factor too.

I agree with Dr. Day who spoke about -- he's
a neurologist who's seen hundreds of boys with
Duchenne. His data is similar to the historical as
how boys decline, which there was a study done by
UCLA. So I --

DR. ALEXANDER: Thank you. Thank you.
MR. DUPREE: Benjamin Dupree. I voted yes.

DR. ALEXANDER: Can you just speak into the microphone a little bit more? Thank you.

MR. DUPREE: Sorry. Benjamin Dupree. I voted yes, the reasoning being that, specifically, with the 6-minute walk test, I think that given how much boys with muscular dystrophy want to continue to walk, that I just don't see that there would bias in deciding to not take the test per se.

DR. GREEN: Mark Green. I voted no. I don't believe that these assessments give a full and adequate assessment of the disabilities of the condition.

DR. HOFFMAN: Richard Hoffman. I voted yes. I think there was plenty of potential for bias but no real evidence of any bias, so we really don't know. And I would say that it's just speculation that there was.

DR. ALEXANDER: Thank you very much. Those are very helpful comments.

So there were comments regarding the fact that this was open label and the panelists would
have loved to have seen a blinded adjudication of outcome. There were concerns regarding the fact that some control patients were deemed unable to do a 6-minute walk test and concerns regarding whether or not they were truly unable to do so.

Another panelist felt there were no concerns about motivation for the boys and more concern about difficulty of using historical controls and all of the biases that we cannot measure.

One panelist felt that there were concerns about the question itself and had trouble knowing how to interpret this to make a firm yes or no answer.

The effect of historical controls is unknowable, also concerns about the potential motivational bias that may be present. More than one panelist commented -- again, we're back to the fact that there was a 6-minute walk time or no 6-minute walk time for a few subjects that had 10-meter data present, and so panelists questioned the objectivity and comparability of the 6-minute walk test.
One felt a predetermined selection criteria were not sufficient to control for biases as open label. One wavered between yes and abstain but didn't believe that patients were extra motivated to maintain mobility, that is that they're sufficiently motivated and thus less of a concern regarding motivational bias.

One felt that there were concern that we're losing grasp with heterogeneity of disease progression, and they felt that it isn't appropriate to analyze the data based on patient's age, and felt that it was more appropriate to analyze based on children's stage of development.

One was disappointed with the data that was analyzed and felt that patients weren't randomized and wasn't convinced that historical controls were comparable, but the real problems is the endpoint itself. It doesn't look at upper body; it only looks at lower body. There are better measures such as for ALS.

One felt there was a differential and believes the FDA should require non-ambulatory arms.
in every DMD trial, lots of things to be studied.

Another voted yes because the 6-minute walk
test was felt to be sufficient. And given how much
patients with DMD want to continue walk, the
panelist didn't see how there could bias in terms
of not taking the test.

One felt that the assessments didn't provide
a full and adequate assessment of the condition.
And the final panelist mentioned as support for
their vote that, yes, that they didn't believe that
there was any real evidence of any bias.

So we'll move on to the next question. So
I'll read the question, but I also want to provide
the panelists a chance to ask clarifying questions
of the FDA prior to the vote.

So the question is, question number 5, What
is the impact of the North Star Ambulatory
Assessment Results on the persuasiveness of the
findings in study 201/202?

Does the NSAA, the North Star Ambulatory
Assessment Results, does the NSAA strengthen the
persuasiveness of the findings in study 201/202?
Does it weaken the persuasiveness of the findings or is there no effect?

So are there any clarifying questions on the part of the panelists for the FDA regarding the wording of this question and its meaning?

Yes, Dr. Gonzales?

DR. GONZALES: Nicole Gonzales. Are we supposed to use all of the data presented by both Sarepta and the FDA or use one or the other?

DR. ALEXANDER: I think you'd be using the totality of evidence that's been discussed and presented today and provided in the briefing packet to you.

Dr. Gordon?

DR. GORDON: The sponsor is asking for permission to clarify something for the record regarding the 6-minute walk test.

DR. ALEXANDER: If there is a specific question on the part of a panelist seeking clarification, then we can pursue that. But if not, I'd like to proceed with this vote unless there are questions of clarification for the FDA.
regarding the wording of question 5.

Yes, Dr. Nuckolls?

DR. NUCKOLLS: So not regarding the wording, but I see on slide, whatever, 85, 86, the comparison of the slope of North Star in the treated and control, and the standard deviation error bars look like they're completely overlapping. But I'm wondering is there any evidence of a statistically significant difference between --

DR. BASTINGS: The answer is no.

DR. ALEXANDER: Are there any further questions of clarification for the FDA regarding the wording of question 5?

(No response.)

DR. ALEXANDER: If not, we'll proceed to vote.

So once again, what is the impact of the North Star Ambulatory Assessment Results on the persuasiveness of the findings in study 201/202? Do these results, A) strengthen -- I'm sorry. I guess it is A, B and C.
So do these results, A, strengthen the persuasiveness; B) weaken the persuasiveness; or C) no effect?

(Vote taken.)

DR. CHOI: Everyone has voted. The vote is now complete.

DR. ALEXANDER: Thank you. So why don't we begin with the first --

DR. CHOI: For the record, we have 2 votes for A, strengthen; 5 votes for B, weaken; and 6 votes for C) no effect.

DR. ALEXANDER: Thank you. So we'll begin with the first voting member on this side, and please state your name, your vote, and a very brief explanation of why you voted as you did.

DR. HOFFMAN: Richard Hoffman, and I voted no effect, C, basically because there was a complete difference of opinion on this matter between the sponsor and the FDA. And it's kind of who do you believe and how do you interpret the data.

DR. ALEXANDER: Please continue.
DR. GREEN: Yes. Mark Green. Mine also is an error. I wanted C as well. Please change my vote because I don't think it had any persuasive evidence either direction.

DR. ALEXANDER: Okay. So for the record, Dr. Green is voting C, that it had no effect.

MR. DUPREE: Benjamin Dupree. I voted C. I just don't see one way or the other that it influences the persuasiveness.

MS. GUNVALSON: I'm Cheri Gunvalson. I voted A. I felt the sponsor had a strong point.

DR. ALEXANDER: Can you just specify the basis for that?

MS. GUNVALSON: Well, when Dr. McDonald explained the findings, as others have said, there are two sets of data. I mean, I wavered between C and A, but that's where I'm at.

DR. KRYSCIO: Richard Kryscio. I voted on the weakened side because of the graph I saw produced by the FDA, two parallel lines, one line below the other, indicating that the historical control group was not comparable.
It helped convince me the historical control
group is not comparable to the randomized patients.
And there's a large variability in there showing no
statistical difference between the two parallel
lines. And finally, that has to do with the sample
size that was chosen, I'm sure. And this
measurement, NSAA, is closer to a functional rating
scale than is the 6-minute walk test.

DR. ROMITTI: Paul Romitti. I voted C, no
effect and for reasons discussed.

DR. NUCKOLLS: Glen Nuckolls. I voted B,
weakened. So the North Star test measures function
of many of the same muscle groups as the 6-minute
walk. And since there is no statistically
significant difference between the treated and
control groups, that in my mind weakens the
strength of the 6-minute walk data.

DR. FOLEY: Reghan Foley. I voted C, no
effect. For me, it didn't lessen or weaken or
strength the results. For me, the main issue to
preserve ambulation.

DR. KESSELHEIM: Aaron Kesselheim. I voted
C, no effect. I was also moved by the slides with the really, really large error bars, again, indicating probably just the small numbers of patients in this comparison.

But, these are all sort of historical control comparisons performed after the trial had already sort of been started and going along, so some of them might turn out positive; some of them negative. And for me, this ended up being one of the many different things that were tested, and therefore, to me, overall had no effect.

DR. ALEXANDER: Caleb Alexander. I felt that it weakened the evidence that was presented primarily because the NCAA, as I understand it, assesses -- is comprised of many more measures than a single dimensionality. So I guess that leads me to feel a little bit more confident in it as an overall assessment.

There was also a difference at baseline, which I guess raised concerns for me about the comparability of the two groups at baseline. But the trajectories, the trend lines are virtually
indistinguishable, and the confidence intervals overlap.

So for me, I think I would have been more convinced about the evidence in 201 and 202 even though those studies, the primary endpoints, as I understood them, were not achieved. I would have been more confident about the longer term follow-up data that was presented and the open label had the NSAA been more compelling.

**DR. ONYIKE:** Chiadi Onyike. I voted no. As already mentioned, the NSAA is a more comprehensive measure than the 6-minute walk test or the 10-minute test. But in any case, neither the FDA, nor the sponsor is claiming a statistically significant difference between the groups on this measure.

**DR. GONZALES:** Nicole Gonzales. I voted no for reasons already mentioned.

**DR. OVBIAGELE:** Bruce Ovbiagele. I voted no for reasons already mentioned.

**DR. ALEXANDER:** Okay. Thank you very much. So for those that voted no effect primarily felt
that they didn't see that this influenced things one way or another.

They were moved by -- one was moved -- one panelist mentioned being influenced by the slides with the large error bars, probably indicating small numbers of patients within the comparisons.

These are all historical comparisons performed after the trial had been started as some might turn out to be positive, some negative. But it turned out as one of many things that were tested.

Those that felt that the NSAA data strengthened the results of studies 201 and 202 felt that the sponsor had a strong point. One panelist mentioned having wavered between no effect and strengthens.

Those that felt that the data weakened the results of the 201 and 202 felt that there were two parallel lines; one was lower than the other. This helped convinced one panelist that the historical control was not comparable.

The results of large variability, no
statistically significant difference, large variation was felt partly due to sample size. NSAA was felt to be closer to a functional rating scale than the 6-minute walk test. It measures function of many of the muscle groups as a 6-minute walk test, so since no difference, this was felt to weaken the association.

It was also pointed out that this was a more comprehensive measure and that neither the FDA or the sponsor is claiming that there was a significant difference between groups on this measure.

So thank you very much for that. And moving right along, we'll move to question 6, which is, what is the impact of the other tests of physical performance such as rise time, 10-meter run/walk on the persuasiveness of findings in study 201/202?

So a very similar question, but in this case, we're discussing not the North Star Ambulatory Assessment but the other test of physical performance: rise time and 10-meter run/walk as two examples of those.
Are there any questions clarifying this question for the FDA; that is, do the panelists have any questions for the FDA about what's being asked?

(No response.)

DR. ALEXANDER: Okay. Very good. So we'll move to voting then. Once again, the question is, What is the impact of the other test of physical performance such as rise time or 10-meter run/walk on the persuasiveness of findings in study 201 and 202?

Does it strengthen the persuasiveness of the findings, does it weaken the persuasiveness of the findings, or is there no effect?

(Vote taken.)

DR. CHOI: Everyone has voted. The vote is now complete. For the record, we have 1 vote for A, strengthen; 2 votes for B, weaken; 10 votes for C, no effect.

DR. ALEXANDER: Thank you. So why don't we begin with Dr. Hoffman? If you could state your name, and your vote and a brief justification or
explanation of why you voted as you did for the record.

   DR. HOFFMAN: Richard Hoffman. And I voted C, no effect because of the same reasons from the previous question.

   DR. ALEXANDER: And those reasons were?

   DR. HOFFMAN: Well, in my opinion, there were differences of opinion between the FDA and the sponsor. And I really didn't think one or the other proved the case one way or the other for that particular testing.

   DR. ALEXANDER: Thank you. Dr. Green?

   DR. GREEN: Yes. I voted C too because I think these represent too small of a sampling error to be convincing about the disability caused by the condition.

   DR. ALEXANDER: Just so I understand you that they represented too small a sampling error?

   DR. GREEN: Sampling the -- there's a lot of overlap between the muscles involved in those two tests, so I think they don't represent the totality of the muscle disorder.
DR. ALEXANDER: Thank you. Mr. Dupree?

MR. DUPREE: Benjamin Dupree. I voted C, no effect. I don't really see that these influence persuasiveness one way or the other because, based on the testimony, it seems like -- I can't see a real correlation between these and the 6-minute walk test.

MS. GUNVALSON: Cheri Gunvalson. I voted A. I believe Dr. McDonald gave a good presentation on how rise time affects ability to walk, and I thought it strengthened it.

DR. KRYSCIO: Richard Kryscio. I voted no effect. These, I viewed as secondary outcomes and it didn't factor into my opinions on this. And there was certainly disagreement between sponsor and the FDA.

DR. ROMITTI: Paul Romitti. I voted C, no effect for the same reasons just explained. There's agreement on how to handle rise time between the FDA and the sponsor. And also, 10-meter walk run, I don't think really adds much to the outcome assessment here.
DR. NUCKOLLS: Glen Nuckolls. I voted no effect. So I get Craig McDonald's point that its ability to rise and not time to rise, but that's just one component of the North Star. But I give that kind of a little bit of strengthen. And then the data from the FDA, it showed there's really no difference in 10-meter walk with the other way, so they kind of cancelled out.

DR. FOLEY: Reghan Foley. I voted C, no effect for reasons already stated. These are secondary outcomes. It didn't really strengthen or weaken the results, in my eyes.

DR. KESSELHEIM: Aaron Kesselheim. I also voted no effect because the secondary outcomes didn't clearly show evidence one way or other. And given the very small sample size, I don't think that there is much that they add one way or other on the main question.

DR. ALEXANDER: Caleb Alexander. I felt that they weakened the results or conclusions one reaches about studies 201/202 primarily because I think the -- in this type of setting where there's
questions about the adequacy of the historical controls and the -- I mean, the amount of dystrophin produced, the adequacy of the historical controls and the relationship between the dystrophin production and outcomes assessed, I would have liked to have seen more convincing evidence of the effect of the study drug on these outcomes.

I think in particular, looking at the experience of individuals over time by age influenced me to feel that these weaken the findings.

DR. ONYIKE: Chiadi Onyike. I voted weaken as well for the reasons -- firstly, for the reasons that Dr. Alexander has explained. But also taking into account Dr. McDonald's explanation, I think that at the end of the day, you still have to control for either age at baseline or age at illness onset if you wish to account for illness duration.

I don't think that you can look at these time-dependent measures independent of some
adjustment for age. And unfortunately, the sample is not large enough to successfully do that. But I think anyone would agree that in a large enough sample, you would be remiss not to control for age.

DR. GONZALES: Nicole Gonzales. I voted no effect. In the absence of a concurrent control group, it makes it very difficult for me to interpret the results of any of the secondary outcome measures.

DR. OVBIAGELE: Bruce Ovbiagele. I voted no effect even though I thought it slightly diminished the effect. But I think there's enough conflict about the interpretation of how to look at this that I thought on balance overall, the effect, if anything, was very minimal.

DR. ALEXANDER: Okay. So those that felt that it strengthened the association felt that rise time affects the ability to walk and that there was a good rationale for why these might be linked.

Panelists that felt that this weakens the persuasiveness of the associations, I should say in studies 201/202, felt that a collateral information
is very important, especially in this setting where
questions have been raised about the primary
endpoints and the 6-minute walk test results.

There was a comment that at the end of the
day, you have to control for age at baseline or
illness onset and that one can't look at these
measures without adjustment for age. But the
sample isn't large enough to do so, that is to
adjust for age.

Then, for those that felt there was no
effect, reasons to support that included that there
are differences in opinion between the FDA and the
sponsor. Neither proved a case one way or the
other for that particular testing. A lot of muscle
is involved between these two tests so that they
don't represent the totality of muscles involved in
this disorder.

Panelists felt that they don't see that
these tests influence the persuasiveness one way or
the other, that there was disagreement with how to
handle the rise time between the FDA and the
sponsor, that the 10-meter test doesn't add much to
Another panelist made the point that they get the point that it's the ability to rise, not time to rise that give some strength in the data that was provided by the FDA.

Panelists felt that these are secondary outcomes and therefore didn't strengthen or weakened the associations -- or the persuasiveness of the findings of studies 201/202, that the evidence regarding these outcomes didn't clearly show evidence one way or another; that there was a small sample size that didn't add much; that in the absence of a concurrent control group, difficult to interpret any of these secondary outcome measures.

So those were some of the rationales for those panelists that felt that there was no effect here.

The last question is a voting question, which is whether or not the clinical results of the single historically-controlled study, that is study 201/202 provide substantial evidence, i.e., evidence from adequate and well-controlled studies
or evidence from a single highly persuasive, adequate and well-controlled study that is accompanied by independent findings, that substantiate efficacy that eteplirsen is effective for the treatment of DMD.

So here again, are there questions to clarify this for the FDA?

(No response.)

DR. ALEXANDER: Are there clarifying questions on the part of the panelist?

(No response.)

DR. ALEXANDER: If not, then we'll move to voting. Once again, the question is, do the clinical results of the single historically-controlled study, study 201 -- I'm sorry. There's a question? Yes?

DR. ONYIKE: Yes. Forgive me.

DR. ALEXANDER: Can you identify yourself please?

DR. ONYIKE: My name is Chiadi Onyike. To what extent are we to incorporate into this question the testimony of the families, the boys
and their families?

(Applause.)

DR. ONYIKE: From my reading of the question, it would seem narrowly worded towards the actual statistical results. So I just want some clarification on that point.

DR. ALEXANDER: Can the FDA address that question, please?

DR. WOODCOCK: Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk.

(Applause.)

DR. WOODCOCK: So the statutory standard is more or less as described there, but there is flexibility, and that's where we should take the views of the community into account.

DR. ONYIKE: Sorry. If I might just follow on. So if I understand you correctly, this question, as worded, is really about statistics; is that correct?

DR. ALEXANDER: Would it be fair to suggest
that you should take into account the totality of information in the briefing packet and what's been discussed today?

DR. WOODCOCK: I think that's fair. The standard is adequate and well-controlled trials. That's what's in the statute. But we are instructed to have flexibility in how we interpret that based on the medical need. So I think, Dr. Alexander, that's a fair summation.

Bob wants to say something.

DR. TEMPLE: There are lots of questions raised about the study, whether there was improper influence of the fact that people knew what the study was and all that kind of stuff.

You heard testimony from patients who said very explicitly that they didn't think that would alter the level of effort that people made. So those kinds of factors are certainly things that are up for discussion.

You know, whether it's persuasive or not, whether the study is persuasive enough, that has a lot to do with the study design and what was
measured, size of the treatment effect and all those things. But you heard testimony that might affect your views on the quality of the endpoints, on the importance of lack of blinding, and all kinds of stuff like that.

DR. ALEXANDER: Dr. Unger?

DR. UNGER: I think with the majority of the patients here, we have an incredible advantage that we -- I mean, in my time with the FDA, it's unprecedented to have basically all of the patients here. So that's an important advantage that we have.

One of the things that you can do is try to reconcile what you've heard from the patients with the data that you've seen presented by the company. We're hearing patients are improving, doing things next year that they didn't do last year. And you have to figure out if you can reconcile that with the actual hard data that you've been analyzing today.

DR. ALEXANDER: Yes? Please state your name and question for the record for the FDA clarifying
this question.

DR. ROMITTI: Paul Romitti. This is directed to Dr. Woodcock because when I look at this question and I think of the first one we discussed, you're talking about two different -- there are some overlap in subjects, but you're talking about two different groups, particularly with the controls.

So I want to understand if we are to consider the dystrophin results, which were tested on some different people than in the one or two, or we just talking about the other part of the study?

DR. WOODCOCK: This is the full approval question, and that is based on the empirical results in the clinic. I agree with what Dr. Unger said. They're not based on the persuasiveness of a surrogate endpoint. They're based on the persuasiveness of the trial that was done.

DR. ALEXANDER: Thank you. One more question of clarification. Please state your name for the record.

DR. OVBIAGELE: Bruce Ovbiagele. Because I
would have two different answers to the questions. One would be objective; one would be subjective. And it's how to reconcile both in the same question here that I guess is the issue.

DR. ONYIKE: This is Chiadi Onyike. If I may quickly add to that, the question twice mentions "well controlled," and as you've heard repeatedly, people have said that they have trouble the control. So this "well controlled" phrase, in a sense, tips or constrains the question.

DR. TEMPLE: I understand a lot of people don't like historically-controlled trials. They're not sure they believe they're well controlled. Our regulations since 1970 have said that a historical-controlled trial can be a well-controlled study, an adequate and well-controlled study.

The question here goes to, do you think, under the circumstances, that it was? Do you think the way they selected them was right? Do you think the way analyzed them was right; good enough to make it an adequate and well-controlled study?
That's the question.

DR. DUNN: Yes --

DR. TEMPLE: Historically-controlled trials have been the basis for approval, sometimes in sort of obvious cases; sometimes in cases that aren't quite as obvious.

DR. DUNN: Yes. Billy Dunn. I want to reiterate all of these issues. I think it's very important to take into account the testimony you heard here today because you heard half of the comparison. You heard from the patients in the 201/202 trials.

They're being compared to a historical control. One of the reasons that I opened up the meeting, and many others reiterated the issues that I abruptly spent so much time talking about what substantial evidence is and what adequate and well-controlled studies are, so that you can sort out whether or not the evidence provided from this study, with the information that you have at hand here from the patients as well as what's provided by the -- what you referred to as more objective
results, rises to the standard that it creates substantial evidence of effectiveness, which again most traditionally is provided by two adequate and well-controlled trials.

We did not set out to refute the notion that the historical control was unacceptable by design. I think we took pains to actually illustrate that that was potentially acceptable.

What we've done is describe to you the concerns that the team had that have to do with the comparability of that control, the acceptability of the use of that control.

So the issue here is that substantial evidence question of whether or not in comparison with the group, with all the issues that we've heard and everything you've heard today, it serves to reach that level of evidence.

DR. ALEXANDER: Thank you. Are there any other final questions clarifying this question before we move to voting?

(No response.)

DR. ALEXANDER: Okay. So we'll move to
voting then, and I'll read the question. If you've
voted once, please do so again. And the question
is as follows:

Do the clinical results of the single
historically-controlled study, study 201/202,
provide substantial evidence, that is evidence from
adequate and well-controlled studies or evidence
from a single highly persuasive adequate and
well-controlled study that is accompanied by
independent findings that substantiate efficacy,
that eteplirisen is effective for the treatment of
DMD?

(Vote taken.)

DR. CHOI: Everyone has voted. The vote is
now complete. We have 3 yes, 7 no, 3 abstentions.

DR. ALEXANDER: Thank you. Why don't we
begin with Dr. Hoffman? If you can state your name
and your vote for the record and a brief
explanation of why you voted as you did.

DR. HOFFMAN: Richard Hoffman. And I voted
to abstain and the reason was, is I was basically
just torn between my mind and my heart. And I
don't want to make type 1 error, and I don't make a
type 2 error.

DR. ALEXANDER: Thank you. Dr. Green?

DR. GREEN: Mark Green. I also abstained
because I'm uncomfortable by the language of the
question because I think it's a bit leading even
though I recognize that's the answer that's
requested of us, because I don't believe that an
external control is customary in a study like this
at all, so I can't say I'm in favor of that.

But I'm very fearful that we'll leave here
with some sort of stalemate between the FDA and the
panel, where I'm still quite sympathetic and
persuaded by the public's presentations.

MR. DUPREE: Benjamin Dupree. I voted yes
because I can't really reconcile the difference
between the testimony that was given suggesting
that the boys' recovering abilities, I
don't -- living with Duchenne, I don't understand
how that's even possible.

But at the same time, this study doesn't
prove from a -- like it doesn't provide what I
think is adequate evidence to support all this testimony that I'm seeing and hearing.

MS. GUNVALSON: Cheri Gunvalson. I voted yes. I believe there's substantial evidence in supporting this.

(Applause.)

DR. KRYSCIO: Richard Kryscio. I voted no. It's not a well-controlled study. I was not convinced that the data was there to basically approve something on the basis of one poorly controlled trial.

DR. ROMITTI: Paul Romitti. I voted to abstain. Like the other panelists before me, I was conflicted with this vote because I do see limitations. And as a scientist, I cannot say that this study -- and answer the question as written -- was adequate and well controlled for a number of reasons.

But I also was moved by the testimony, the public testimony as well. And I'm also concerned that we keep getting more and more information about why there wasn't a placebo-controlled trial.
I'd asked for clarification earlier on in the meeting about when Sarepta was told or asked to do a placebo-controlled trial and received a date of several years ago. And I'm surprised that -- and I feel like maybe that they needed to consider that. Now, we hear maybe they didn't have enough drug.

So more information keeps coming out, so I'm uncomfortable -- as much as I'd like to say yes, I'm uncomfortable with the evidence to date to say yes. I'm moved by the public testimony, but I'm not as uncomfortable to just say no. I think there's still room to work here.

DR. NUCKOLLS: Glen Nuckolls. I voted no. I thought that there were significant concerns regarding the ability to draw valid conclusions from this design of an externally-controlled comparison.

DR. FOLEY: Reghan Foley. I voted yes. As a pediatric neuromuscular specialist, for me, there's substantial evidence that there's amelioration of the clinical phenotype of Duchenne...
dystrophy. I believe that more data is needed, and I also believe that looking at other biomarkers, as Professor Partridge pointed out, would very helpful as well. But I did feel that the phenotype was clearly ameliorated.

DR. KESSELHEIM: Aaron Kesselheim. I voted no. I felt like a historically-controlled study could provide substantial evidence, but this one did not both in its results and its design. I felt like it could therefore be used potentially as supportive. But the original controlled study, placebo-controlled study, the 12 patients was negative. So if it was going to be supportive or secondary, it was going to be secondary to something that did not show an effect.

Then I was also confused -- I was also confused a little bit by the fact that there did appear to be evidence from the audience from more patients that were presented here from some of these newer studies and some of these extension studies.

So I think that there is still information
to learn about this drug. But as the data currently stand, it doesn't appear to me that this historically-controlled study provides substantial evidence.

DR. ALEXANDER: Caleb Alexander. I voted no. I just felt that this wasn't a well-controlled study and that the ways that the controls were selected and analyzed didn't meet the threshold that I would consider to be adequate and well controlled.

We heard criteria for what constitutes a well-controlled study. And even if the study was well controlled, I have concerns regarding the conclusions reached about the efficacy of eteplirsen.

DR. ONYIKE: Chiadi Onyike. I voted no. Basically, the findings do not support a conclusion of yes, at least on the statistical grounds and scientific grounds. And unfortunately, what I would consider meaningful evidence or testimony from the families is not properly measured in the study.
So I hope that in the future that the field will incorporate measures of function. Someone alluded to ALS fields. There are other fields. I work also in the dementia field where caregiver outcomes are routinely included in the clinical trials. I think there needs to be a move in that direction so what you report are not considered soft outcomes. I also hope you would consider, as a community, participating fully in controlled trials so that you're not in this position in the future.

(Audience interrupts.)

DR. ALEXANDER: I'm sorry, please. We have to continue with the explanation.

DR. ONYIKE: My apologies. I don't mean --

(Audience interrupts.)

DR. ALEXANDER: I'm sorry. The audience --

DR. ONYIKE: Let me speak to that, please.

DR. ALEXANDER: No, actually, I'd like to move on.

DR. ONYIKE: Let me speak to it. I made the comment, please. Please.
DR. ALEXANDER: No.

(Audience interrupts.)

DR. ONYIKE: I'm sorry. I didn't mean to be critical or lecturing. What I meant to say -- what I meant to address was the --

DR. ALEXANDER: Thank you. May we have the -- Dr. Gonzales?

DR. GONZALES: Nicole Gonzales. I voted no. The placebo portion of the study wasn't positive on the primary outcome measures, and I had issues with the historical control for secondary clinical endpoints.

DR. OVBIAGELE: Bruce Ovbiagele. I voted no. I thought it wasn't a well-controlled study at all. If I had to vote based on the testimony I heard, if this was a before and after question, definitely based on all that I heard, the drug definitely works, but the question was framed differently.

DR. ALEXANDER: Thank you. So I'd like to just for the record summarize the comments that I've heard.
(Audience interrupts.)

DR. ALEXANDER: I'd like to try to get this entered in to the record and not adjourn the meeting prematurely. So out of respect for all of the individuals that are here, I request that you allow for me to summarize briefly the comments that we've heard thus far.

So those that voted yes felt that one couldn't reconcile the differences between testimony that was given suggesting boys were recovering abilities, didn't understand how that was possible, but the study didn't provide what was felt to be adequate evidence to support all of this testimony that the panelists were seeing.

They felt that there was substantial evidence that the phenotype clearly improved, but there was an encouragement for the collection of more data, including biomarkers.

Individuals that voted no felt that it was not a well-controlled study, that the data wasn't there to approve something on the basis of one poorly controlled trial. There were significant
concerns raised about the ability to draw valid conclusions from this type of external comparison.

One panelist commented that the historical control could provide sufficient information but that this one did not and was also confused by the fact there appear to be evidence from newer studies or extension studies. And the panelist felt that more information would be helpful to learn about this product.

One felt that there wasn't -- that this wasn't a well-controlled study, so here again that the ways the controls were selected and analyzed didn't meet the threshold that they felt would constitute to be adequate and well controlled.

We heard criteria for what constitutes a well-controlled study. A panelist commented that even if it was well controlled, that there was reason to question the conclusions regarding efficacy that were reached.

A panelist commented that based on scientific and statistical grounds, what they would consider meaningful testimony from the families was
not optimally assessed in the study and that
caregiver outcomes are routinely included in
randomized trials in dementia, and that this might
be pursued in DMD. And one panelist also commented
that the placebo portion of the study was not
positive on outcome measures.

Those that abstained, one panelist felt that
he was torn between his mind and his heart. He
doesn't want to make a type 1 error but doesn't
want to make a type 2 error either.

One panelist was uncomfortable by the
language of the question and felt that it was a
little leading and didn't feel that external
control is -- that having an external control is
customary, wouldn't favor that; but one panelist
noted that they feared that we would leave with a
stalemate between the FDA, and they said the panel,
but I imagine they meant the sponsor, maybe not.

One panelist noted that they do see
limitations, that they didn't feel that they could
answer the question affirmatively, but they were
also moved by the public testimony and also
concerned that more and more information -- they were concerned with the additional information about why there wasn't a placebo-controlled trial and that they had asked for that information early in the meeting and then told that the date was, I believe, in 2011 that Sarepta was encouraged to pursue an RCT. That panelist felt uncomfortable with evidence to-date to say yes but they were moved by the public testimony.

Before we adjourn, I would like to give the opportunity to the FDA, if there are any final comments from the FDA?

DR. DUNN: Billy Dunn, FDA. The emotion and passion in the room during the discussion is clear. And I mentioned at the beginning of the day that we listen and we listen carefully. And although I recognize there's great concern about the discussion and the results of the votes, I assure you that we listened very carefully.

We've heard some very meaningful testimonies today, and we've observed the panel be highly influenced by that testimony. I assure you that we
will take the information we've learned here today
under very serious consideration as we adjourn this
meeting.

**Adjournment**

**DR. ALEXANDER:** Thank you. And I'd just
like to add my thank you to the patients and
friends and family, the members of the general
public. Many of you exerted a tremendous effort to
get here, and I appreciate your participation.

Also, I'd like to thank the FDA staff and
scientists, the sponsor for the enormous amount of
work that all of you and your colleagues have
performed in order to make today possible. I'd
also like to thank the conference center staff as
well for helping to host this event.

Once again, thank you for your contribution
to today's meeting. The meeting is now adjourned.
Panel members, please take all your personal
belongings with you as the room is cleaned at the
end of the meeting today. 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 for
your participation.

(Whereupon, at 7:37 p.m., the meeting was
adjourned.)