1 FOOD AND DRUG ADMINISTRATION

2 CENTER FOR DRUG EVALUATION AND RESEARCH

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6 PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

7 ADVISORY COMMITTEE (PCNS)

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13 Monday, April 25, 2016

14 8:00 a.m. to 7:37 p.m.

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18 College Park Marriott Hotel and Conference Center

19 Chesapeake Ballroom

20 3501 University Boulevard East

21 Hyattsville, Maryland

22

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Moon Hee V. Choi, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**

9 **ADVISORY COMMITTEE MEMBERS (Voting)**

10 **G. Caleb Alexander, MD, MS**

11 *(Chairperson)*

12 Associate Professor of Epidemiology & Medicine

13 Johns Hopkins School of Public Health

14 Center for Drug Safety and Effectiveness

15 Baltimore, Maryland

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17 **Nicole R. Gonzales, MD**

18 Associate Professor

19 University of Texas-Houston Medical School

20 Department of Neurology - Stroke Program

21 Houston, Texas

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1 **Mark W. Green, MD, FAAN**
2 Professor of Neurology, Anesthesiology, and
3 Rehabilitation Medicine
4 Director of Headache and Pain Medicine
5 Icahn School of Medicine at Mt Sinai
6 New York, New York
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8 **Richard P. Hoffmann, PharmD**
9 *(Consumer Representative)*
10 Drug Information Consultant/Medical Writer
11 Hernando, Florida
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13 **Richard J. Kryscio, PhD**
14 Professor, Statistics
15 Chair, Biostatistics
16 University of Kentucky
17 Lexington, Kentucky
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1 **Chiadi U. Onyike, MD**
2 Associate Professor of Psychiatry and Behavioral
3 Sciences
4 Division of Geriatric Psychiatry and
5 Neuropsychiatry
6 Department of Psychiatry and Behavioral Sciences
7 The Johns Hopkins University School of Medicine
8 Baltimore, Maryland
9
10 **Bruce I. Ovbiagele, MD, MSc, MAS**
11 Professor and Chairman of Neurology
12 Medical University of South Carolina
13 Charleston, South Carolina
14
15 **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**
16 **ADVISORY COMMITTEE MEMBER (Non-Voting)**
17 **Mark Gordon, MD**
18 *(Industry Representative)*
19 Director, Clinical Development and Medical Affairs
20 General Medicine/Central Nervous Systems
21 Boehringer Ingelheim Pharmaceuticals, Inc.
22 Ridgefield, Connecticut

1 **TEMPORARY MEMBERS (Voting)**

2 **Benjamin Dupree**

3 *(Patient Representative)*

4 Dallas, Texas

5

6 **A. Reghan Foley, MD**

7 Staff Clinician

8 Neuromuscular and Neurogenetic Disorders of

9 Childhood Section, Neurogenetics Branch

10 Division of Intramural Research

11 National Institute of Neurological Disorders of

12 Stroke (NINDS)

13 National Institutes of Health (NIH)

14 Bethesda, Maryland

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16 **Cheri Gunvalson, RN, MS**

17 *(Patient Representative)*

18 Clinical Assistant Professor

19 University of North Dakota, College of Nursing

20 Grand Forks, North Dakota

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1 **Aaron S. Kesselheim, MD, JD, MPH**

2 Associate Professor of Medicine

3 Harvard Medical School

4 Director, Program on Regulation, Therapeutics, and

5 Law (PORTAL)

6 Division of Pharmacoepidemiology and

7 Pharmacoeconomics

8 Brigham & Women's Hospital

9 Boston, Massachusetts

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11 **Glen Nuckolls, PhD**

12 Program Director and Executive Secretary

13 Interagency Muscular Dystrophy Coordinating

14 Committee, Neurogenetics Cluster

15 Division of Extramural Research, NINDS, NIH

16 Bethesda, Maryland

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1 **Paul Romitti, PhD**

2 Professor

3 Department of Epidemiology and Interdisciplinary

4 Program in Toxicology

5 University of Iowa

6 Iowa City, Iowa

7

8 **FDA PARTICIPANTS (Non-Voting)**

9 **Janet Woodcock, MD**

10 Director

11 CDER, FDA

12

13 **John Jenkins, MD**

14 Director

15 Office of New Drugs (OND), CDER, FDA

16

17 **Ellis Unger, MD**

18 Director

19 Office of Drug Evaluation I (ODE-I)

20 OND, CDER, FDA

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22

1 **Robert Temple, MD**

2 Deputy Director

3 ODE-I, OND, CDER, FDA

4

5 **Billy Dunn, MD**

6 Director

7 Division of Neurology Products (DNP)

8 ODE-I, OND, CDER, FDA

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10 **Eric Bastings, MD**

11 Deputy Director

12 DNP, ODE-I, OND, CDER, FDA

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14 **Ronald Farkas, MD, PhD**

15 Clinical Team Leader

16 DNP, ODE-I, OND, CDER, FDA

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1 C O N T E N T S

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C O N T E N T S (continued)

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

2 AGENDA ITEM PAGE

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

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. ALEXANDER: Good morning, and thank you
6 for joining us today. I'd like to first remind
7 everyone to please silence your cell phones,
8 smartphones, and any other devices if you have not
9 already done so. I'd also like to identify the FDA
10 press contact, Sandy Walsh.
11 Sandy, if you are present, can you please
12 stand and identify yourself? Thank you.
13 My name is Dr. Caleb Alexander. I'm the
14 chairperson of the Peripheral and Central Nervous
15 System Drugs Advisory Committee meeting, and I'll
16 now call this meeting to order. We'll start by
17 going around the table and introducing ourselves.
18 Let's start down here on the right with Dr. Gordon,
19 please.
20 DR. GORDON: Good morning, everyone. My
21 name is Mark Gordon. I am the industry
22 representative, and I work for Boehringer Ingelheim

1 Pharmaceuticals.
2 DR. HOFFMAN: Richard Hoffman. I'm a
3 pharmacist and medical writer, and I'm the consumer
4 representative for this meeting.
5 DR. GREEN: Mark Green. I'm a professor of
6 neurology, anesthesiology, and rehabilitation
7 medicine at Mount Sinai School of Medicine.
8 MR. DUPREE: I'm Benjamin Dupree, a
9 23-year-old with Duchenne muscular dystrophy, here
10 serving as a patient representative.
11 MS. GUNVALSON: I'm Cheri Gunvalson. I'm
12 the mother of a 24-year-old son with Duchenne. I'm
13 also a nurse and a clinical nursing professor at
14 the University of North Dakota.
15 DR. KRYSCIO: Good morning, I'm Richard
16 Kryscio. I'm from the University of Kentucky, and
17 I'm a biostatistician.
18 DR. ROMITTI: Good morning. I am Paul
19 Romitti, a professor of epidemiology and toxicology
20 at the University of Iowa.
21 DR. NUCKOLLS: Good morning. I'm Glen
22 Nuckolls. I'm program director for the muscular

1 dystrophies at NIH at the Neurology Institute, and
2 I'm the designated federal official for the
3 Interagency Muscular Dystrophy Coordinating
4 Committee.
5 DR. FOLEY: Good morning. I'm Reghan Foley.
6 I'm a pediatric neuromuscular specialist. I work
7 at the Neuromuscular and Neurogenetic Disorders of
8 Childhood Section of the Neurogenetics Branch of
9 the NINDS at NIH.
10 DR. KESSELHEIM: Good morning. I'm Aaron
11 Kesselheim, an associate professor of medicine at
12 Brigham & Women's Hospital in the Division of
13 Pharmacoepidemiology and Pharmacoeconomics at
14 Harvard Medical School.
15 DR. ALEXANDER: And once again, I'm Caleb
16 Alexander. I'm an associate professor of
17 epidemiology and medicine at Johns Hopkins
18 Bloomberg School of Public Health.
19 DR. CHOI: Moon Hee Choi, designated federal
20 officer.
21 DR. ONYIKE: Chiadi Onyike, associate
22 professor of psychiatry at Johns Hopkins.

1 DR. GONZALES: Nicole Gonzales, associate
2 professor of neurology at the McGovern Medical
3 School at the University of Texas in Houston.
4 DR. OVBIAGELE: Bruce Ovbiagele, professor
5 and chair of neurology at the Medical University of
6 South Carolina.
7 DR. FARKAS: Ronald Farkas, clinical team
8 leader at the Division of Neurology Products at
9 FDA.
10 DR. DUNN: I'm Billy Dunn. I'm the director
11 of the Division of Neurology Products at FDA.
12 DR. BASTINGS: Eric Bastings, deputy
13 director of the Division of Neurology Products at
14 the FDA.
15 DR. UNGER: Ellis Unger, director, Office of
16 Drug Evaluation I at the FDA.
17 DR. JENKINS: Good morning. I'm John
18 Jenkins. I'm the director of the Office of New
19 Drugs in CDER at FDA.
20 DR. TEMPLE: Good morning. Bob Temple,
21 deputy director of ODE-I.
22 DR. WOODCOCK: And I'm Janet Woodcock. I'm

1 head of the drug center at FDA.
2 DR. ALEXANDER: Thank you.
3 For topics such as those being discussed at
4 today's meeting, there are often a variety of
5 opinions, some of which are quite strongly held.
6 Our goal is that today's meeting will be a fair and
7 open forum for discussion of these issues and that
8 individuals can express their views without
9 interruption.
10 Thus, as a gentle reminder, individuals will
11 be allowed to speak into the record only if
12 recognized by the chairperson. We look forward to
13 a productive meeting.
14 In the spirit of the Federal Advisory
15 Committee Act and the Government in the Sunshine
16 Act, we ask that the advisory committee members
17 take care that their conversations about the topic
18 at hand take place in the open forum of the
19 meeting. We are aware that members of the media
20 are anxious to speak with the FDA about these
21 proceedings. However, FDA will refrain from
22 discussing the details of this meeting with the

1 media until its conclusion. Also, the committee is
2 reminded to please refrain from discussing the
3 meeting topic during breaks or lunch. Thank you.
4 Now I'll pass it to Moon Hee Choi, who will
5 read the conflict of interest statement.
6 **Conflict of Interest Statement**
7 DR. CHOI: The Food and Drug Administration
8 is convening today's meeting of the Peripheral and
9 Central Nervous System Drugs Advisory Committee
10 under the authority of the Federal Advisory
11 Committee Act of 1972.
12 With the exception of the industry
13 representative, all members and temporary voting
14 members of the committee are special government
15 employees or regular federal employees from other
16 agencies and are subject to federal conflict of
17 interest laws and regulations.
18 The following information on the status of
19 this committee's compliance with federal ethics and
20 conflict of interest laws, covered by but not
21 limited to those found at 18 U.S.C. Section 208, is
22 being provided to participants in today's meeting

1 and to the public. FDA has determined that members
2 and temporary voting members of this committee are
3 in compliance with Federal Ethics and Conflict of
4 Interest laws.
5 Under 18 U.S.C. Section 208, Congress has
6 authorized FDA to grant waivers to special
7 government employees and regular federal employees
8 who have potential financial conflicts when it is
9 determined that the agency's need for a particular
10 individual's services outweighs his or her
11 potential financial conflict of interest.
12 Related to the discussions at today's
13 meetings, members and temporary voting members of
14 this committee have been screened for potential
15 financial conflicts of their own as well as those
16 imputed to them, including those of their spouses
17 or minor children, and for purposes of 18 U.S.C.
18 Section 208, their employers. These interests may
19 include investments, consulting, expert witness
20 testimony, contracts, grants, CRADAs, teaching,
21 speaking, writing, patents and royalties, and
22 primary employment.

1 Today's agenda involves new drug application
2 206488, eteplirsen injection for intravenous
3 infusion sponsored by Sarepta Therapeutics for the
4 treatment of Duchenne muscular dystrophy in
5 patients who have a confirmed mutation of the DMD
6 gene that is amenable to exon 51 skipping. This is
7 a particular matters meeting during which specific
8 matters related to Sarepta Therapeutics NDA will be
9 discussed.
10 Based on the agenda for today's meeting and
11 all financial interests reported by the committee
12 members and temporary voting members, no conflict
13 of interest waivers have been issued in connection
14 with this meeting. To ensure transparency, we
15 encourage all standing committee members and
16 temporary voting members to disclose any public
17 statements that they have made concerning the
18 product at issue.
19 With respect to FDA's invited industry
20 representative, we would like to disclose that
21 Dr. Mark Gordon is participating in this meeting as
22 a non-voting industry representative acting on

1 behalf of regulated industry. Dr. Gordon's role at
2 this meeting is to represent industry in general
3 and not any particular company. Dr. Gordon is
4 employed by Boehringer Ingelheim.
5 We would like to remind members and
6 temporary voting members that if the discussions
7 involve any other products or firms not already on
8 the agenda for which an FDA participant has a
9 personal or imputed financial interest, the
10 participants need to exclude themselves from such
11 involvement, and their exclusion will be noted for
12 the record. FDA encourages all participants to
13 advise the committee of any financial relationships
14 that they may have with the firm at issue. Thank
15 you.
16 DR. ALEXANDER: Thank you very much. We'll
17 now proceed with the FDA's introductory remarks
18 from Dr. Billy Dunn, director of the Division of
19 Neurology Products.
20 **FDA Introductory Remarks - Billy Dunn**
21 DR. DUNN: Thank you, Dr. Alexander.
22 Good morning. Welcome to all our committee

1 members, guests who have traveled here, and all the
2 folks who are joining us by electronic means for
3 this important meeting.
4 I'm in a somewhat unusual situation of
5 delivering remarks that will, in part, be the same
6 as or similar to remarks I made to this committee
7 quite recently, when we gathered almost exactly
8 five months ago, to discuss drisapersen for the
9 treatment of Duchenne muscular dystrophy.
10 While perhaps familiar to some, I am certain
11 that we have quite a few people joining us today
12 who were not present in November of last year, and
13 many of my comments bear repetition.
14 I want to thank the committee for your
15 willingness to be here, your eagerness to consider
16 the important topics we will discuss today, and
17 your forthrightness in sharing with us your
18 perspectives on the application under
19 consideration. I want to especially thank the
20 public attendees, both in person and those joining
21 us by audio or video broadcast, for their
22 commitment to finding a treatment for Duchenne

1 muscular dystrophy.

2 I particularly want to note and thank the

3 patients with DMD who are joining us today. I am

4 extraordinarily impressed with the turnout for this

5 committee meeting as I look out over the audience

6 today, and I was particularly impressed as I walked

7 in through the public spaces of all the patients

8 with DMD who are here. Thank you for being here.

9 Your efforts to be here are invaluable and

10 tremendously appreciated.

11 On a broader note than just this committee

12 meeting today, I want to take a moment to mention

13 how much we here at FDA appreciate our interaction

14 with the DMD community. We have been very engaged

15 with the scientific and advocacy leaders in this

16 area, which I am confident has resulted in an

17 improved understanding for both the community and

18 ourselves.

19 The tireless efforts of the DMD community

20 resulted in a proposed draft guidance, as many here

21 know, from an advocacy group that was submitted to

22 us for our consideration. I am happy to be able to

1 say that building on that effort, we published our
2 own draft guidance in June of last year for DMD, a
3 major accomplishment and I think a source of great
4 collaborative progress for the field.
5 We are here today, after a delay due to
6 severe weather in January that has tried the
7 patience of many, to discuss eteplirsen for the
8 treatment of Duchenne muscular dystrophy in
9 patients with mutations amenable to exon 51
10 skipping.
11 There is without question a profound unmet
12 medical need in DMD. We have no approved
13 treatments for this disease. We are highly
14 sensitive to the urgency needed for the development
15 of an improved treatment for Duchenne. Before
16 briefly describing some of the issues we will ask
17 you to discuss today, I want to stress that we have
18 not made any final decisions on the approvability
19 of this application.
20 Many believe that we are here today to
21 render a final decision on approvability. We are
22 not. We are here to have a discussion and gain

1 input from you, the committee members.
2 The information in your background packages
3 are preliminary reviews only that do not yet take
4 into account today's proceedings. Though you may
5 encounter preliminary conclusions and
6 recommendations concerning approvability and, as
7 you have seen in your background materials, they
8 may often describe grave concerns about the data
9 put forth in support of the ostensible
10 effectiveness of eteplirsen.
11 Those conclusions and recommendations should
12 be viewed as just that, preliminary. They should
13 not be viewed as the opinion or conclusion of
14 anyone other than the author of the individual
15 review, and they should not be viewed as
16 necessarily indicative of our final decision.
17 The reason we are here today is to gain your
18 input into some of the challenging issues we have
19 confronted during our review process so that we may
20 incorporate it into our ultimate decision on
21 approvability.
22 As will be discussed in detail during the

1 presentations you will hear today, eteplirsen is
2 theorized to lead to clinical benefit by
3 potentially increasing the production of a
4 truncated form of dystrophin. The natural form of
5 dystrophin, a key muscle protein, is profoundly
6 deficient in DMD, and the gene defect giving rise
7 to this deficiency is thought to the be the primary
8 underlying cause of the disease.
9 How much of this truncated dystrophin
10 eteplirsen is designed to produce could be helpful
11 is an open question. The committee will recall its
12 previous discussion in November during which the
13 committee expressed concern about the plausibility
14 of clinical benefit being derived from extremely
15 small increases in dystrophin on the order of
16 post-treatment absolute values of less than
17 1 percent of normal.
18 As you will hear today, we are again
19 confronted with post-treatment absolute values in
20 that range.
21 You will also hear of concerns concerning
22 limitations on the interpretation of these post-

1 treatment absolute values. Of possible relevance
2 to this question of how much dystrophin could
3 convey clinically meaningful benefit is the fact
4 that some patients with Duchenne have very small
5 amounts of the naturally occurring truncated
6 dystrophin that does not appear to be associated
7 with an appreciable slowing of muscle degeneration.
8 Some patients with a related form of
9 muscular dystrophy, Becker muscular dystrophy,
10 naturally produce such a truncated dystrophin and
11 have only mild disease. In these Becker patients,
12 the truncated dystrophin is present at levels often
13 50 to 100 percent of what normal dystrophin would
14 be.
15 The sponsor conducted three studies of
16 eteplirsen, two small exploratory studies, which
17 are referred to as study 28 and study 33, to assess
18 the potential of eteplirsen to increase dystrophin
19 expression, and a single small 12-patient clinical
20 study, which is referred to as study 201/202 but is
21 really a single study with two phases, to further
22 assess the extent to which eteplirsen might

1 increase expression of dystrophin and to explore
2 the potential clinical benefit.
3 As I said, though an initial phase of
4 study 201/202, the 201 portion, was placebo-
5 controlled, dividing the patients into 3 groups of
6 4 patients each, the second phase of the study was
7 an open-label extension.
8 Despite strong encouragement from FDA to
9 conduct an adequately powered, randomized, placebo-
10 controlled trial or trials to assess the clinical
11 effect of eteplirsen, the sponsor asserted that the
12 conduct of such a trial would be prohibitively
13 difficult.
14 Given the sponsor's assertions, FDA advised
15 the sponsor on the issues involved in an attempt to
16 compare the open-label extension data to data from
17 a natural history cohort identified post hoc that
18 might serve as an external control, emphasizing
19 that interpretation of such a comparison could be
20 difficult and that the acceptability of this
21 approach would be a matter for NDA review.
22 The sponsor identified two DMD patient

1 registries, one in Italy and one in Belgium, as a
2 source of external data, and conducted a post hoc
3 comparison of the data from the open-label
4 extension to data from these two registries.
5 The sponsor offers as primary support for
6 approval a comparison of ambulatory ability based
7 on 6-minute walk distance in these two groups. As
8 is clear from the background documents provided to
9 you, we have significant concerns about the
10 validity of this comparison.
11 It is these two primary issues, one, the
12 data concerning dystrophin, we will ask you to
13 discuss and vote on whether there is substantial
14 evidence from adequate and well-controlled studies
15 as required under the Food, Drug, and Cosmetic Act
16 that eteplirsen induces a production of dystrophin
17 to a level that is reasonably likely to predict
18 clinical benefit.
19 Two, the data concerning the historically
20 controlled comparison of ambulatory ability, we'll
21 ask you to discuss and vote on whether substantial
22 evidence of effectiveness has been provided as

1 required under the Food, Drug, and Cosmetic Act by
2 the clinical results of a single historically
3 controlled efficacy study. It is these two issues
4 that we primarily bring to the committee for your
5 discussion.
6 Why do we focus on these two issues in this
7 manner? We must, as required by law, determine
8 whether there is substantial evidence of
9 effectiveness of eteplirsen in order to consider
10 approval. Both of these issues have the potential
11 to provide such evidence if the data are
12 interpretable.
13 Substantial evidence of effectiveness is a
14 crucial concept and one worth spending a few
15 moments discussing. Prior to 1962, evidence of
16 effectiveness was not even required for drug
17 approval, it was only necessary to demonstrate
18 safety.
19 The 1962 Kefauver-Harris amendments to the
20 Food, Drug, and Cosmetic Act included a provision
21 requiring manufacturers of drug products to
22 establish a drug's effectiveness by substantial

1 evidence, an important advance that signaled the
2 beginning of the modern era of drug development and
3 regulation.
4 Senator Kefauver considered these amendments
5 requiring evidence of effectiveness his finest
6 achievement in consumer protection, and their
7 adoption laid the groundwork for FDA's development
8 of an evidence-based model for drug evaluation
9 decisions that stands as the global standard.
10 Their importance is impossible to overstate.
11 "Substantial evidence of effectiveness,"
12 these words are not vague words to be defined
13 according to whim or fashion. Substantial evidence
14 was defined in Section 505(d) of the Act as, quote,
15 "Evidence consisting of adequate and well-
16 controlled investigations, including clinical
17 investigations, by experts qualified by scientific
18 training and experience to evaluate the
19 effectiveness of the drug involved on the basis of
20 which it could be fairly and responsibly be
21 concluded by such experts that the drug will have
22 the effect it purports or is represented to have

1 under the conditions of use prescribed,
2 recommended, or suggested in the labeling or
3 proposed labeling thereof." It's a mouthful, but
4 that's what it is.
5 Adequate and well-controlled investigations
6 are further defined in FDA regulations as having
7 various characteristics, one of which is the use of
8 a design that permits a valid comparison with a
9 control to provide a quantitative assessment of
10 drug effect. Of the generally recognized controls
11 that are recognized in regulations, all are
12 concurrent except for the last one known as
13 historical control.
14 The regulations note that, quote, "Because
15 historical control populations usually cannot be as
16 well assessed with respect to pertinent variables,
17 as can concurrent control populations, historical
18 control designs are usually reserved for special
19 circumstances.
20 "Examples include studies of diseases with
21 high and predictable mortality, for example certain
22 malignancies, and studies in which the effect of

1 the drug is self-evident, for instance general
2 anesthetics or drug metabolism."
3 You will note that investigations are
4 referred to in the law, investigations being
5 plural. It has long been FDA's position that
6 Congress generally intended to require at least two
7 adequate and well-controlled studies, each
8 convincing on its own, to establish effectiveness.
9 The usual requirement for more than one
10 adequate and well-controlled investigation reflects
11 the need for independent substantiation of
12 experimental results. Independent substantiation
13 of a favorable result protects against the
14 possibility that a chance occurrence in a single
15 study will lead to an erroneous conclusion that a
16 treatment is effective.
17 Any clinical trial may be subject to
18 unanticipated, undetected systemic biases. These
19 biases may operate despite the best intentions of
20 sponsors and investigators and may lead to flawed
21 conclusions.
22 There are circumstances in which FDA may

1 rely on something less than at least two adequate
2 and well-controlled studies. In 1997, the FDA
3 Modernization Act, which we refer to as FDAMA,
4 amended Section 505(d) of the Act to make it clear
5 that FDA may consider data from one adequate and
6 well-controlled clinical investigation and
7 confirmatory evidence to constitute substantial
8 evidence if FDA determines that such data and
9 evidence are sufficient to establish effectiveness.
10 Reliance on only a single adequate and
11 well-controlled efficacy study to establish
12 substantial evidence of effectiveness is also a
13 possibility. Because reliance on two adequate and
14 well-controlled studies is generally more secure
15 than reliance on one similarly persuasive study,
16 FDA has generally relied on only a single adequate
17 and well-controlled efficacy study to support
18 approval only in cases in which a single
19 multicenter study of excellent design provided
20 highly reliable and statistically strong evidence
21 of an important clinical benefit, such as an effect
22 on survival, and a confirmatory study would have

1 been difficult to conduct on ethical grounds.
2 Examples of typical characteristics of a
3 single adequate and well-controlled study that
4 could make the study adequate to support an
5 effectiveness claim include those that you see
6 here. These are examples, they are not
7 requirements, but they have a common theme in that
8 such characteristics serve to increase the
9 reliability of the reported findings and might
10 allow the results of a single study to effectively
11 provide a similarly persuasive amount of
12 information as two independent adequate and
13 well-controlled studies.
14 Because of the inherent vulnerabilities
15 involved in reliance on a single study, it is
16 critical that the possibility of an incorrect
17 outcome be considered and that all the available
18 data be examined for their potential to either
19 support or undercut reliance on a single trial.
20 Generally, when discussing substantial
21 evidence of effectiveness, we are discussing
22 evidence based on primary assessment of clinically

1 meaningful effects, and such substantial evidence
2 may result in a conventional approval.
3 Accelerated approval is a particular type of
4 approval that FDA may grant to a product for a
5 serious or life-threatening disease or condition
6 upon a determination that the product has an effect
7 on a surrogate endpoint that is reasonably likely
8 to predict clinical benefit; or on a clinical
9 endpoint that can be measured earlier than
10 irreversible morbidity or mortality and is
11 reasonably likely to predict an effect on such; or
12 some other clinical benefit taking into account the
13 severity, rarity, or prevalence of the condition
14 and the availability or lack of alternative
15 treatments.
16 FDA has discussed accelerated approval in
17 the context of DMD specifically in our DMD guidance
18 that I mentioned earlier. We have indicated that
19 biomarkers that reliably reflect the health and
20 amount of skeletal muscle may, if supported by
21 sufficient scientific evidence and acceptable
22 analytical methods, be used as endpoints to support

1 accelerated approval of a new DMD drug. Such a
2 biomarker would have to be reasonably likely to
3 predict clinical benefit in order to be acceptable
4 as a basis for accelerated approval.
5 Concerning accelerated approval, it is
6 crucial to recognize that the evidentiary standards
7 for effectiveness are not lower for biomarker or
8 intermediate clinical endpoints used to support
9 accelerated approval. Substantial evidence of an
10 effect on those biomarker or intermediate clinical
11 endpoints must be demonstrated.
12 As we discussed, substantial evidence comes
13 from adequate and well-controlled investigations
14 and is evidence that the drug will have the effect
15 it purports or is represented to have. Accelerated
16 approval concerns the character of the endpoints,
17 not the strength of the results on those endpoints.
18 An effect on an endpoint supporting
19 accelerated approval must be an effect on an
20 endpoint that in its character is reasonably likely
21 to predict clinical benefit, and in its
22 persuasiveness provide substantial evidence of

1 effectiveness from adequate and well-controlled
2 trials just as substantial evidence of
3 effectiveness on a clinically meaningful endpoint
4 from adequate and well-controlled trials supports
5 conventional approval.
6 It is a common misconception that data not
7 sufficiently persuasive for conventional approval
8 can be shifted over to consideration for
9 accelerated approval. Accelerated approval is not
10 a rescue strategy for suggestive data that are
11 insufficient for conventional approval.
12 Although it is possible to consider
13 suggestive data, insufficient on their own for
14 conventional approval, in a supportive role to
15 complement substantial evidence of effectiveness
16 that has been provided for a biomarker, accelerated
17 approval cannot be used to compensate for weak or
18 inconsistent clinical findings.
19 It is more common to consider accelerated
20 approval when data on the biomarker are available
21 in advance of clinical results. If unconvincing
22 clinical results are reported in the face of what

1 are thought to be promising biomarker results, this
2 would tend to weaken confidence that the biomarker
3 results are reasonably likely to predict benefit.
4 As I mentioned previously, under the proper
5 circumstances, FDA regulations recognize that
6 historical control studies can be considered
7 adequate and well-controlled studies and used to
8 support approval. There are many issues to
9 consider with the interpretability of such studies
10 as discussed in an international guideline
11 concerning choice of control group in clinical
12 trials.
13 These issues are of critical importance when
14 considering any historical control trial, and so
15 Dr. Bob Temple will present a separate discussion
16 of this important topic that will help inform
17 issues specific to the eteplirsen application that
18 will be subsequently discussed by the review team.
19 Following my remarks, the applicant,
20 including consultants from the academic and
21 advocacy arenas, will make a series of
22 presentations supportive of eteplirsen's benefit,

1 and you will have a chance to ask clarifying
2 questions.
3 After a short break, we will reconvene for a
4 series of presentations from the FDA, beginning
5 with comments from Dr. Janet Woodcock, the director
6 of the Center for Drug Evaluation and Research.
7 Next, as I noted, Dr. Temple, the center's
8 deputy director for clinical science and the acting
9 deputy director of the Office of Drug Evaluation I,
10 will discuss issues to consider with external
11 control studies.
12 Following that, Dr. Ron Farkas, a team
13 leader in the neurology division, and Dr. Ash Rao,
14 the acting chief of the Laboratory of Applied
15 Biochemistry, will present a detailed discussion of
16 the multi-disciplinary team's concerns and findings
17 regarding the eteplirsen application.
18 Dr. Eric Bastings, the neurology division's
19 deputy director, will provide concluding remarks.
20 You will again have a chance to ask clarifying
21 questions.
22 After a break for lunch, we will have the

1 open public hearing followed by discussion and
2 questions to the committee. The FDA presentations
3 will highlight a number of issues that we'll ask
4 you to discuss and respond to, including the
5 strengths and weaknesses of findings regarding
6 dystrophin, the strength and weaknesses of the
7 clinical findings, the relative impacts of various
8 clinical outcome measures that were assessed, and
9 of fundamental importance, the comparability of the
10 eteplirsen and control groups. We have provided
11 discussion topics and questions to help frame your
12 discussion following the presentations.
13 As you consider the background materials, I
14 remind you that we have been made aware that some
15 of you have been approached by outside
16 organizations; some of you on the committee have
17 received materials that were ostensibly germane to
18 these proceedings.
19 I think you've been informed by the advisory
20 committee staff, and I've been asked to remind you,
21 that you are to consider only the background
22 documents that were provided to you by the

1 applicant and by the agency, not any other
2 materials that were provided to you by outside
3 agencies.
4 I urge the committee to keep several things
5 in mind as the remainder of the meeting gets
6 underway. It might fairly be asked, although you
7 say no final decision on approvability has been
8 made, isn't that disingenuous. Your background
9 materials are highly critical and you describe
10 fundamental concerns about the application. Why
11 was this even accepted for review?
12 It is important to note that when we were
13 involved in discussions with Sarepta about
14 application submission, it was our understanding
15 that dramatic increases of dystrophin were being
16 observed, as much as 50 percent of normal values,
17 and that this was accompanied by dramatic and
18 unprecedented clinical stabilization of patients.
19 Such reports, unless obviously dismissible on face,
20 clearly would warrant careful review.
21 An important, perhaps the important, issue
22 we bring to you for discussion, is comparability.

1 You will hear both scientific and emotional
2 commentary and testimony about how eteplirsen
3 treated patients are doing. We do not challenge
4 that. The concerns we raise about the application
5 are not trying to suggest that what these patients
6 are reporting, completing, achieving, living is not
7 real. It clearly is.
8 What we are concerned about is the accuracy
9 and acceptability of the comparison being made to a
10 group that could differ in important ways, both
11 known and unknown, from the eteplirsen treated
12 patients.
13 Please, as what will surely be an emotional
14 discussion might tend towards a suggestion that we,
15 the FDA, do not accept these reported improvements
16 as important, know that if these results were from
17 a well-designed, interpretable trial, there likely
18 wouldn't be much to talk about. We likely wouldn't
19 even be here.
20 We come to you with sincere concerns not
21 because we take some perverse delight in keeping
22 new medicines from those who urgently need them, as

1 has been somewhat bizarrely suggested by some, but
2 because it is our, we the FDA, and you our advisory
3 committee, collectively, it is our fundamental
4 responsibility to ensure, as required by law, that
5 the treatments we approve are effective.
6 Keep your focus on the comparability of
7 these groups and whether we can truly conclude that
8 what these few eteplirsen treatment patients are
9 experiencing is clearly outside the natural
10 variability of the disease.
11 There are many people here. It's
12 extraordinarily important that everybody that has
13 come is here, and it's extraordinarily important
14 that those who are watching from afar are doing so.
15 As Dr. Alexander noted, it's entirely possible that
16 emotions will run high. People are passionate and
17 invested, and we understand that.
18 Investment can influence perception. I have
19 no doubt that if I had DMD and I was receiving
20 eteplirsen, that I would attribute all of the
21 success of my activities to eteplirsen. I may be
22 right about that. The issue is whether or not we

1 have a group to which we can compare reliably.
2 I am truly glad everyone is here. The
3 outpouring of support for those with this disease
4 is nothing short of spectacular. It provides
5 needed context and awareness, but anecdote and
6 emotion do not change the data with which we are
7 confronted, no matter the attendance.
8 Whether we have 1,000 here or only 1, the
9 same data will be there to consider. And I know
10 that each of you will render the same
11 scientifically sound opinions and judgments to a
12 full room that you would to an empty one.
13 Speaking of a full room, even as I am deeply
14 moved by those here in attendance, it makes me
15 realize that I have a message for those, many who
16 are watching these proceedings, both with Duchenne
17 and even for illnesses other than Duchenne,
18 especially diseases that occur only in small
19 numbers, and those folks who have diseases that do
20 not have highly organized support systems and
21 advocacy machines capable of assembling such a
22 massive effort as that which we see today.

1 It must be frightening to think that there
2 is no way that you can be heard. I want to
3 reassure you, it is not the volume of the message,
4 but the content. We listen, and we listen closely.
5 To all those out there watching, your voice is
6 heard.
7 We have brought to you important issues for
8 which we seek your advice. These are complicated
9 issues, and we will be asking you to vote on
10 several questions, and we'll be listening very
11 carefully to your discussion of all these topics.
12 The content of your discussion and explanation of
13 your reasoning is of great importance to us.
14 Again, no final decision has been made on
15 approvability, and we very much look forward to the
16 insights you will provide. We have convened this
17 committee because we feel that a final decision
18 requires your input and advice.
19 Thank you for the substantial efforts you
20 have made in preparing for and attending this
21 meeting, and thank you for the important work you
22 will do today. It is vital.

1 Dr. Alexander, thank you for the time to
2 offer my comments, and I return the proceedings to
3 you.
4 DR. ALEXANDER: Thank you, Dr. Dunn.
5 Both the Food and Drug Administration and
6 the public believe in a transparent process for
7 information-gathering and decision-making. To
8 ensure such transparency at the advisory committee
9 meeting, FDA believes that it is important to
10 understand the context of an individual's
11 presentation.
12 For this reason, FDA encourages all
13 participants, including the sponsor's non-employee
14 presenters, to advise the committee of any
15 financial relationships that they may have with the
16 firm at issue, such as consulting fees, travel
17 expenses, honoraria, and interests in the sponsor,
18 including equity interest and those based upon the
19 outcome of the meeting.
20 Likewise, FDA encourages you at the
21 beginning of your presentation to advise the
22 committee if you do not have any such financial

1 relationships. If you choose not to address this
2 issue of financial relationships at the beginning
3 of your presentation, it will not preclude you from
4 speaking. We will now proceed with Sarepta
5 Therapeutics presentations.
6 **Applicant Presentation - Shamim Ruff**
7 MS. RUFF: Dr. Alexander, members of the
8 advisory committee, and FDA, good morning. My name
9 is Shamim Ruff. I'm the head of regulatory affairs
10 and quality at Sarepta. I am honored today to
11 begin our formal presentation on eteplirsen for the
12 treatment of Duchenne muscular dystrophy, or DMD.
13 Before we begin, however, permit me two
14 brief but important acknowledgements. First, those
15 who suffer from DMD, many of them here today, and
16 in particular the 12 boys who allowed us to follow
17 them for 4 years in our trials, this important
18 dialogue today is for you.
19 Second, to those so deeply committed to
20 combating this crippling disease, including
21 caregivers and investigators, we thank you for your
22 continued commitment.

1 We at Sarepta fully recognize that what we
2 are about to present to you is not a traditional
3 data set. It must be understood that DMD is an
4 enormously challenging disorder to study due to its
5 rarity, heterogeneity, and rapid progression.
6 Nevertheless, in that context, we believe we have
7 done both important and groundbreaking work.
8 Our colleagues at the FDA have
9 understandably challenged us on several fronts. We
10 both appreciate and welcome that challenge as it
11 has caused us to think more deeply about DMD and we
12 believe raises important questions for future
13 research.
14 Today, we will address the key issues head
15 on and offer you data that demonstrate three
16 important findings.
17 First, eteplirsen unequivocally produces de
18 novo dystrophin protein. Second, the external
19 control is valid, reliable, and reflective of the
20 natural history of DMD. And third, eteplirsen
21 treated boys behave differently to DMD natural
22 history with a large magnitude of benefit on the

1 6-minute walk test as well as loss in ambulation.
2 We look forward to a robust, scientific, and
3 candid discussion and thank the panel for your
4 participation in helping us advance the
5 understanding of this disease.
6 DMD is a pediatric X-linked recessive
7 neuromuscular disease caused by mutations in the
8 DMD gene that prevent the production of functional
9 dystrophin protein. Dystrophin plays a vital role
10 in the structure, function, and preservation of
11 muscle cells, and in its absence, patients follow a
12 predictable disease course.
13 Boys develop muscle weakness in their first
14 few years of life, then in early adolescence lose
15 the ability to walk. Complications from this loss
16 of ambulation have a major cascading effect,
17 including scoliosis, compromised respiratory
18 function, and premature death, usually in the
19 mid-to late-20s.
20 As you will hear in a moment from
21 Dr. Mercuri, despite welcome improvements in the
22 standard of care, including steroids and other

1 supportive measures, there is a profound unmet
2 medical need for DMD patients with no approved
3 therapies in the United States.
4 The proposed indication for eteplirsen is
5 for the treatment of DMD patients with mutations in
6 the dystrophin gene amenable to exon 51 skipping.
7 The proposed dose is 30 milligrams per kilogram,
8 administered as weekly IV infusions.
9 Here's a breakdown of the genetic mutations
10 for the 9 to 12,000 boys who suffer from DMD in the
11 United States. The dark blue section indicates a
12 subset of DMD boys who are amenable to skipping
13 exon 51 and can be treated with eteplirsen. This
14 represents 13 percent of the total DMD population
15 and shows how eteplirsen is one of the first
16 examples of precision genetic medicine.
17 In order to understand how eteplirsen works,
18 let's look at the underlying disease process and
19 how the drug addresses it. Here's a small section
20 of the dystrophin gene where we see a normal
21 reading of the mRNA by the ribosome, which in turn
22 produces a dystrophin protein of normal length.

1 But here's what happens in a DMD patient,
2 deletion mutations in the dystrophin gene disrupt
3 the reading frame; thus, the ribosome can't
4 correctly read the message after the deletion,
5 which results in little to no dystrophin, the
6 hallmark of the severe DMD phenotype.
7 Eteplirsen induces a skipping of exon 51,
8 restoring the reading frame and allowing the
9 production of a shorter, internally deleted,
10 functional dystrophin protein.
11 As I previously mentioned, Sarepta comes to
12 you today with a non-traditional data set, a small
13 study with a natural history comparator. Yet,
14 while the package may be unusual, it is not
15 unprecedented in the rare disease arena. Of note,
16 although the study size is not extensive, it is a
17 4-year clinical follow-up period that gives us both
18 robust insight into the benefit of eteplirsen.
19 So how did we arrive at this point? Over
20 the past couple of years, we've participated in
21 more than a dozen meetings with the FDA to agree on
22 an appropriate data package for an NDA submission.

1 Let me highlight a significant series of events
2 that transpired during that time.
3 First, due to the initial encouraging
4 results of our phase 2 study, the DMD community
5 expressed an unwillingness to participate in a
6 placebo-controlled study. This led FDA, in April
7 of 2014, to ask us to obtain natural history or
8 external control data for comparison. We did so,
9 and comparison to that untreated external group now
10 serves as the primary basis for establishing
11 clinical efficacy.
12 In December 2015, the agency made a request
13 for an additional 4-year data. The results were
14 striking with a 162-meter benefit in the 6-minute
15 walk test. In addition, Kaplan-Meier estimates
16 showed a 17 percent loss of ambulation for
17 eteplirsen compared to 85 percent for the untreated
18 external control.
19 Because of this new and important data, FDA
20 in February of 2016 extended the PDUFA date by
21 3 months. In recognition of this unique set of
22 circumstances, Sarepta is seeking accelerated

1 rather than full approval.
2 FDASIA, the Food and Drug Administration
3 Safety and Innovation Act, was signed into law in
4 July of 2012. It expands and encourages the
5 broader use of accelerated approvals beyond HIV and
6 oncology to rare diseases such as DMD.
7 Importantly, FDASIA also requires FDA to
8 seek patient input during drug development as well
9 as during the review of the application. Of note,
10 accelerated approval allows for an acceptable
11 degree of uncertainty regarding the anticipated
12 benefit.
13 Essentially, there are three specific
14 requirements of accelerated approval, and
15 eteplirsen meets them all. First, the disease has
16 to be serious and life-threatening and the drug has
17 to provide benefit over existing therapies. We
18 clearly meet this.
19 Second, approval must be based on either a
20 surrogate endpoint or an intermediate endpoint that
21 are reasonably likely to predict benefit. For
22 eteplirsen the FDA provided us two pathways, either

1 dystrophin as a surrogate endpoint or the 6-minute
2 walk test as an intermediate endpoint.
3 Lastly, post-marketing confirmatory studies
4 are required to verify the anticipated effect.
5 Sarepta in consultation with the FDA agreed to
6 conduct two post-marketing confirmatory studies.
7 We recognize that accelerated approval does
8 not change the statutory requirements, and today we
9 will demonstrate to you that the endpoints selected
10 are appropriate and we have established substantial
11 evidence of effectiveness.
12 So what constitutes substantial evidence of
13 effectiveness? It's important to note that the
14 intent of the statute was to reduce the chance of
15 an incorrect conclusion. Ideally, a randomized
16 placebo-controlled study would be used, but this is
17 not essential.
18 Historical controls can be considered
19 adequate and well controlled, particularly in the
20 rare disease arena, and there are multiple examples
21 of FDA approvals based on small studies and
22 historical controls.

1 Before we go through the rest of the
2 presentation, I'd like to address a few of the
3 concerns FDA raised and offer our position
4 beginning with dystrophin. First of all, in the
5 week 180 analyses, FDA only focused on the Western
6 blot results and discounted the immunohistochemical
7 results.
8 Experts suggest there is no single
9 definitive method for dystrophin quantification.
10 Multiple complementary methods are required to get
11 the full picture. Dr. Kaye will describe how
12 eteplirsen showed significant dystrophin production
13 using three distinct methods.
14 Second, eteplirsen Western blot results were
15 compared to published references going back to 1989
16 that were semi-quantitative at best. The more
17 appropriate comparison is to look at fold increases
18 over baseline within the same assay.
19 Finally, they concluded that the quantity of
20 dystrophin produced was not clinically relevant.
21 However, research in the field suggests that even
22 small amounts of dystrophin can have a clinical

1 effect. Of note, this is the first time that a
2 therapeutic has demonstrated an unequivocal
3 increase in dystrophin expression.
4 FDA also identified three main concerns with
5 our 6-minute walk test results. First, they
6 highlighted that study 201 failed to show an
7 advantage over eteplirsen versus placebo for the
8 6-minute walk test at week 24. I'd like to clarify
9 that percent dystrophin fibers was the primary
10 endpoint for that study, not the 6-minute walk
11 test.
12 They also outlined a concern about the use
13 of external control to determine efficacy. The key
14 issue here is the potential for bias due to
15 differences in the two patient populations. To be
16 clear, there were predefined selection criteria for
17 the external control, which were based on the
18 inclusion criteria for the eteplirsen 201 study.
19 Also, the key baseline characteristics were
20 highly comparable, as were the standards of
21 supportive care. They both had up to 4 years of
22 longitudinal data, and 6-minute walk test

1 measurement was according to the same standardized
2 protocol. The FDA guidelines also state that for
3 an external control comparison to be interpretable,
4 the effect size has to be large. We certainly saw
5 a compelling effect size.
6 Finally, we will provide longitudinal
7 comparisons to multiple databases that clearly show
8 eteplirsen-treated boys behaved differently from
9 natural history.
10 As you review the data we will present
11 today, we ask that you keep an open mind and
12 critically evaluate eteplirsen in context of
13 accelerated approval, the rarity of the disease,
14 and the profound unmet need. We know for certain
15 that DMD boys, if left untreated, will progress in
16 their disease with a known risk of serious and
17 fatal consequences.
18 Given this, along with the production of
19 de novo dystrophin protein and the benefits seen on
20 the 6-minute walk test and loss in ambulation is
21 the degree of uncertainty about whether the therapy
22 will result in the anticipated clinical benefit

1 acceptable for accelerated approval.
2 Turning now to the rest of the agenda, we
3 are extremely fortunate to have some of the world's
4 eminent experts in DMD available today. In a few
5 moments Dr. Mercuri, who provided much of the data
6 for the external control, will provide an overview
7 of the disease background and natural history.
8 Dr. Kaye, a pediatric neurologist and
9 interim CEO at Sarepta, will present the efficacy
10 data, followed by Dr. Eliopoulos, senior medical
11 director, who will review the safety data.
12 Dr. Mendell, the principal investigator for the
13 pivotal eteplirsen studies, will provide a clinical
14 perspective on the benefit-risk of eteplirsen. And
15 finally, Dr. Kaye will return to provide concluding
16 remarks.
17 In addition to answer questions, we also
18 have available Dr. Muntoni and Dr. Wilton, who are
19 two of the world's leading experts on dystrophin
20 methodologies; Dr. Muntoni was also the PI for our
21 phase 1 studies; Dr. Kinane, who is a pediatric DMD
22 pulmonary expert; Dr. McDonald, who is a leading

1 DMD natural history expert in the U.S. and study
2 chair of the Synergy Duchenne Natural History
3 study; and last but not least, Dr. Lu, who is our
4 consultant statistician.
5 Please note that after the concluding
6 remarks by Dr. Kaye, there will be a presentation
7 by the Jett Foundation, who requested that we
8 donate a portion of our allotted time for a
9 separate and independent presentation. We are
10 happy to do so.
11 Christine McSherry, executive director of
12 the Jett Foundation and the mother of a boy with
13 DMD, will provide a review of the patient and
14 caregiver reported outcomes collected from
15 eteplirsen trials. And with that, I'm happy to
16 invite Dr. Mercuri to come to the podium and
17 describe the natural history of DMD.
18 **Applicant Presentation - Eugenio Mercuri**
19 DR. MERCURI: Thank you.
20 Good morning. My name is Eugenio Mercuri.
21 I'm a pediatric neurologist working in Rome and
22 coordinator of the Italian Duchenne network. I'm a

1 paid consultant to Sarepta in preparation for this
2 meeting, and I have no direct financial interest in
3 the outcome of the meeting today.
4 As Ms. Ruff explained, Duchenne muscular
5 dystrophy is caused by mutation to the dystrophin
6 gene. In healthy boys, dystrophin is normally
7 expressed and contributes to the protection of
8 muscle fibers during contraction, acting as a
9 molecular shock absorber. In DMD, the absence of
10 dystrophin leads to progressive muscle degeneration
11 with progressive loss of muscle function.
12 Here we see a series of muscle biopsies
13 performed at different ages. The first picture on
14 the left shows a biopsy performed at birth. Even
15 though we know that dystrophin is already absent,
16 the muscle tissue appears normal.
17 As shown in the second picture, already in
18 the first years, there are aspects of inflammation
19 and necrosis with loss of functional muscle tissue
20 that increases over the years, and the major
21 tipping point in the disease progression occurs
22 around the age of 7.

1 At this age, you can see that muscle cells
2 are increasingly replaced by fibrotic tissue and
3 fat. Finally, in the fourth picture of a biopsy
4 performed in an older boy, we see a complete loss
5 of the normal muscle architecture.
6 Clinically, in the first month, there are no
7 obvious clinical signs, but a blood test will
8 reveal elevated CK levels, which is indicative of
9 muscle damage. DMD boys often show some delayed
10 milestones, but the diagnosis is on average after
11 the age of 3 years. At a time when they are
12 supposed to learn to hop, jump, and run, DMD boys
13 have difficulty running and hopping, standing from
14 supine, and in climbing stairs. After the age of
15 7, there is a more rapid decline leading to loss of
16 ambulation in early adolescence.
17 Historically, before the era of steroids,
18 DMD boys did not walk beyond the age of 12, with a
19 median age at loss of ambulation of 9.5 years.
20 Contemporary studies, however, have shown that the
21 median age with current standards of care is
22 between 11 and 13 years, and this is consistent

1 across countries.
2 Similar results were found in several U.S.
3 and EU countries as well as in Japan. Recently, a
4 new global data set from CINRG shows that the
5 median age for loss of ambulation for boys amenable
6 for skipping exon 51 is 12 years.
7 Loss of ambulation is an important endpoint,
8 but we hear from Duchenne boys and their families
9 that even after that, many other important physical
10 functions are progressively affected. At loss of
11 ambulation, boys are generally still able to
12 perform shoulder movements, but later there is a
13 progressive loss of upper limb function. And after
14 the age of 20, arm movements are generally limited
15 to distal movements of the fingers.
16 Respiratory impairment, which declines
17 steadily throughout the patient's life, usually
18 becomes significant enough to require nocturnal
19 ventilation in the patient's 20s, followed by
20 full-time ventilation. Heart muscle is also
21 affected, and despite advances in care, most
22 patients will die from cardiac disease in their

1 mid-20s. The mean survival is approximately
2 27 years.
3 Next, I'll talk about how disease
4 progression is most commonly measured in clinical
5 and research settings. The 6-minute walk test is
6 the most widely used measure in Duchenne
7 intervention or in natural history status. It's an
8 integrated global measure that is affected by
9 strength, endurance, and cardiorespiratory status.
10 As you can see in the video, the test is
11 performed by asking the patients to walk as fast as
12 possible for 6 minutes around a 25-meter course,
13 measuring the distance covered in 6 minutes.
14 The test has been slightly modified for
15 children with Duchenne from the original American
16 Thoracic Society version with introduction of a
17 second examiner that stays close to the patient for
18 safety reasons, as you can see on the video.
19 Another important modification is the use of
20 standardized encouragement to maintain the child's
21 attention and to limit bias. The examiner -- this
22 is very important. The examiner must follow very

1 strict instructions providing the wording and the
2 timing of when the encouragement should be given.
3 In clinical trials and in natural history
4 status, experienced and trained physiotherapists
5 follow very strictly these procedures. As a
6 result, the 6-minute walk test has been found to be
7 a sensitive, reliable, and reproducible outcome
8 measures in a multicenter setting.
9 It also has the highest test/retest
10 reliability of the commonly used measure for
11 Duchenne. And another advantage of the 6-minute
12 walk test is its high correlation with other
13 functional measures.
14 In particular, it shows a correlation with
15 the North Star Ambulatory Assessment. The scale
16 was originally developed as a clinical tool for
17 ambulant Duchenne and has only recently been
18 validated as an outcome measure. Although it's
19 less statistically robust than the 6-minute walk
20 test, it provides important additional clinical
21 information.
22 The scale includes 17 items. Each item is

1 scored from zero, if the boy is unable to perform
2 the task independently, to 2 if he's able to
3 complete the task. The order of the items follows
4 the progression of the disorder. Younger boys on
5 steroids are generally able to complete most
6 activities, but with increasing age, especially
7 after the age of 7, they gradually lose abilities
8 with the predictable disease course from bottom to
9 top.
10 Focus groups with families made a strong
11 point that each of the 17 activities are related to
12 important activities of daily living and losing
13 even one of them represents an irreversible loss
14 that is important and meaningful for their quality
15 of life.
16 Using these tools, we can measure sequential
17 loss of function in Duchenne. For example, rise
18 time is lost at early stage. It's actually the
19 first activity that is lost when boys are still
20 able to walk independently and perform the 6-minute
21 walk test.
22 The 6-minute walk test provides a major

1 functional ambulation, and once boys are unable to
2 complete the test, they are generally not able to
3 walk outdoors or at school anymore. In some cases,
4 the 10-meter test can be measured in these last
5 stages of ambulation and can have a positive value
6 at the time when they score zero on the 6-minute
7 walk test. When happening however, this usually
8 lasts only a few months. At this stage, they are
9 usually only able to perform minimal functional
10 walking at home, often holding on to furniture and
11 walls for safety as the risk of falls and bone
12 fracture is very high.
13 This has caused some confusion in the
14 definition of loss ambulation with different
15 definition in the literature. Moreover, this
16 definition is more challenging in retrospective
17 studies. For example, in the CINRG studies, which
18 allowed for retrospective outcomes, loss of
19 ambulation is defined as patient reported full-time
20 wheelchair use confirmed by the 10-meter test when
21 possible. In contrast, in many prospective
22 studies, including the Italian Telethon and Leuven

1 studies, the loss of ambulation is defined as zero
2 meters on the 6-minute walk test.
3 I will now review what we have learned from
4 recent natural history data. Using the 6-minute
5 walk test, we have been able to identify a number
6 of prognostic factors affecting disease
7 progression. The role of steroids is well-known,
8 but recently, we have been able to identify other
9 factors that affect the rate of decline, such as
10 age, type of mutations, or the values of the
11 6-minute walk test.
12 As I mentioned earlier, boys with Duchenne
13 initially gain in functional activity before
14 experiencing a progressive and irreversible
15 decline. In this study, 191 Duchenne patients were
16 assessed at different ages and followed for 1 year.
17 Patients who were younger than 7 when first
18 assessed improved their 6-minute walk performance
19 after 1 year by nearly 30 meters. In contrast,
20 those who were older than 7 had already started
21 declining by nearly 40 meters after 1 year.
22 This information has been extremely helpful

1 in identifying a more homogeneous declining patient
2 population in more recent studies.
3 Let's focus on the group of 68 patients who
4 were above the age of 7 when they were first
5 assessed. In a follow-on study assessing 6 minute
6 changes over 3 years, we not only confirmed that on
7 average there is a decline in the first year, but
8 also that there was progressive deterioration that
9 became more marked with each increasing year.
10 In addition to age, genetic mutation has
11 also been shown to impact performance on the 6-
12 minute walk test. In this study of 191 patients
13 with Duchenne, some differences in baseline
14 6-minute walk test were observed for different
15 mutation types. The vertical line in the middle of
16 the graph represents the mean values for the whole
17 cohort. When we subdivide the cohort according to
18 the type of mutation, all the different sub-groups
19 were relatively close to the mean, but some
20 differences could be observed. Patients with
21 duplications or point mutations had better
22 performance and on average walked more meters than

1 patients with deletions.
2 Some variations were also observed within
3 the boys with deletions depending on which exons
4 were deleted. Patients with exon deletions
5 amenable to skipping exons 45, 51, or 53 all walked
6 less far, indicating a more severe phenotype. In
7 contrast, patients with deletions amenable to
8 skipping exon 44 walked further at baseline.
9 This is consistent with other reports
10 indicating a milder phenotype for this patient
11 group, and it's probably related to the fact that
12 these patients, unlike other groups with deletions,
13 have low levels of naturally occurring dystrophin.
14 This is also corroborated by a recent CINRG study,
15 which reports that Duchenne patients with deletions
16 amenable to exon 44 have a delay in loss of
17 ambulation of up to 2 years.
18 As clinicians, we are often asked the
19 question, why is it important to maintain 6-minute
20 walk distance. And we have learned that
21 maintaining 6-minute walk test is important because
22 its distance can predict loss of ambulation.

1 This graph shows the results of a study
2 performed on 131 boys with Duchenne followed for
3 over 2 years. The study evaluated the risk of
4 losing ambulation in different sub-groups
5 subdivided according to the 6-minute walk test.
6 Looking from left to right, it's obvious
7 that the risk of losing ambulation increases as the
8 6-walk distance decreases. These results suggested
9 if we are able to maintain or even to slow down the
10 degradation of the 6-minute walk distance, we
11 therefore also decrease the risk of losing
12 ambulation.
13 Maintaining ambulation is of course
14 important per se, but it's also important as loss
15 of ambulation is related to the onset of further
16 progression of other aspects of disability. In a
17 recent French study, a cohort of boys with Duchenne
18 followed for over 20 years was subdivided into
19 3 groups based on age of loss of ambulation.
20 The study showed that boys who lost
21 ambulation at the later stage, after the age of 11,
22 also had a significant delay in the need for

1 ventilation and in the time when they lost the
2 ability to self-feed.
3 I would like to stress how important this
4 chain of events is. If we delay progression in the
5 6-minute walk test, we delay not only loss of
6 ambulation, but also the subsequent events of
7 disease progression, such as loss of self-feeding
8 or need for ventilation.
9 The natural history data I just showed are
10 the results of international efforts to harmonize
11 standards of care between U.S. and Europe that were
12 formally published in 2009. These include the use
13 of steroids, but also provides specific indication
14 on physical therapy and on the management of
15 orthopedic, respiratory, and cardiac risk.
16 In summary, the improvement in standard of
17 care has produced a clear shift in natural history,
18 delaying loss of ambulation and subsequent
19 functional decline, such as respiratory failure,
20 cardiac impairment, and ultimately death.
21 But this is not enough. Despite these
22 improvements, Duchenne is still a rapidly

1 progressive and ultimately fatal disorder. And as
2 a clinician, as part of the Duchenne community, we
3 strongly feel there is therefore an urgent unmet
4 need to find treatments that may further slow down
5 disease progression.
6 Now, I would like to turn the podium over to
7 Dr. Kaye to discuss efficacy of eteplirsen.
8 **Applicant Presentation - Edward Kaye**
9 DR. KAYE: Building on the scientific
10 foundation that Dr. Mercuri just presented, I would
11 like to describe the findings that confirm
12 eteplirsen benefit. We will look at the rationale
13 for development of eteplirsen, an overview of
14 Sarepta's clinical development program, a
15 description of the pharmacodynamic data, the
16 process for choosing the external control, the
17 clinical results, and finally an overview of our
18 confirmatory studies.
19 Let's begin by looking at the rationale for
20 why exon skipping could work in Duchenne muscular
21 dystrophy. As the previous speakers explained,
22 mutations that disrupt the RNA reading frame lead

1 to the production of little to no functional
2 dystrophin and result in the severe DMD phenotype.
3 The concept of exon skipping as a
4 therapeutic strategy is demonstrated through an
5 experiment in nature. In Becker muscular
6 dystrophy, deletion mutations, which maintain the
7 RNA reading frame, enable the production of an
8 internally deleted dystrophin. These in-frame
9 mutations result in a shortened dystrophin protein
10 generally associated with a milder phenotype. Exon
11 skipping aims to produce a protein similar to
12 Becker.
13 FDA has stated in their briefing document
14 that Becker muscular dystrophy patients have high
15 levels of dystrophin, however, after looking at the
16 literature we note a wide range of dystrophin
17 levels, ranging from 2 to 100 percent.
18 Given this wide range of dystrophin
19 expression, researchers over the past 25 years have
20 tried but failed to establish a definitive
21 dystrophin threshold that results in a clinical
22 benefit. What has been established is that the

1 presence of even small amounts of dystrophin may
2 have a clinical impact.
3 For example, Duchenne muscular dystrophy
4 patients amenable to exon 44 skipping express
5 slightly higher levels of dystrophin than the
6 general DMD population and experience a milder
7 phenotype. Ultimately, the most meaningful
8 assessment of dystrophin in a clinical trial is not
9 based on literature values but on increase from
10 baseline. The conclusion was emphasized at a March
11 2015 FDA NIH workshop on dystrophin quantification,
12 as well as in the FDA briefing guidance.
13 We are fortunate to have two academic
14 experts with us today, Dr. Francesco Muntoni and
15 Dr. Steve Wilton, who can answer questions and
16 provide insight on dystrophin quantification.
17 I would now like to take a moment to review
18 our complete DMD clinical program. Eteplirsen was
19 initially evaluated in two phase 1 studies. The
20 first established proof of concept through single
21 intramuscular injection, and the second study
22 tested weekly systemic IV administration at various

1 doses.

2 Having observed increased dystrophin in both
3 phase 1 studies, Sarepta initiated study 201/202.
4 This is the pivotal study, which will be the focus
5 of my presentation today. Enrollment included an
6 ambulatory population between the ages of 7 to
7 13 years.

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

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

21 Study 201 was a 24-week study to evaluate
22 dystrophin expression as a pharmacodynamic

1 endpoint. The study tested eteplirsen at
2 2 systemic weekly IV doses, 30 milligrams per
3 kilogram shown in purple, and 50 milligrams per
4 kilogram shown in green, compared to placebo shown
5 in gray. Dosing was limited to 8 patients at study
6 initiation due to limited drug supply.
7 After week 24, the placebo group was rolled
8 over on to either 30 or 50 milligrams of
9 eteplirsen. Study 202 extended the trial to
10 further evaluate both continuing pharmacodynamic
11 and efficacy endpoints and is ongoing to date.
12 Data from all 12 of these patients were pooled to
13 enable comparison to an external control over
14 4 years.
15 In order to best observe a treatment effect,
16 the 201/202 enrollment criteria were chosen to
17 obtain a homogeneous group of patients that would
18 be predicted to decline. As Dr. Mercuri detailed
19 in his presentation, a number of prognostic factors
20 predict decline in DMD, including a mutation
21 amenable to exon 51 skipping, an age range of 7 to
22 13 years, a stable steroid regimen for at least

1 24 weeks prior to enrollment, and finally a
2 6-minute walk test distance between 180 and
3 440 meters. These same factors drove our
4 enrollment criteria.
5 The pivotal 201/202 studies included several
6 key endpoints. The primary endpoint for study 201
7 was increase in dystrophin protein expression. The
8 primary clinical endpoint for study 202 is the
9 6-minute walk test.
10 Supportive endpoints included mechanism of
11 action by RT-PCR, dystrophin protein production,
12 the NSAA, and the ability to rise from supine.
13 Importantly, we are here today to seek approval
14 based on clinical differences in walking ability in
15 addition to dystrophin production.
16 As I will now show, eteplirsen has a precise
17 mechanism of action as demonstrated by dystrophin
18 production. The most direct measure of
19 eteplirsen's mechanism of action is exon skipping,
20 which was evaluated by RT-PCR and sequencing. The
21 shortened PCR product was identified and sequenced
22 to confirm that the correct newly formed exon

1 junction was present. All biopsied eteplirsen
2 patients produced the expected product,
3 demonstrating that the drug is working as intended.
4 The March 2015 FDA NIH workshop on
5 dystrophin measurement concluded that complementary
6 methods are necessary to provide a complete protein
7 assessment. Western blot was used to quantify
8 dystrophin following extraction of protein from
9 muscle tissue. However, for dystrophin to be
10 functional, it must be localized to the sarcolemmal
11 membrane and only immunohistochemistry can provide
12 this information.
13 Immunohistochemical images were used to
14 assess the percent dystrophin positive fibers
15 providing information on sarcolemmal localization
16 and distribution of dystrophin in muscle tissue.
17 Finally, the immunohistochemical images were
18 assessed by a computer algorithm to measure
19 fluorescence intensity to quantify dystrophin at
20 the membrane. Taken together, these assays provide
21 a comprehensive view of dystrophin expression.
22 Study 201 was designed to test whether dose

1 or duration was most important in the production of
2 dystrophin positive fibers. No significant
3 increase was observed at 12 weeks for the
4 50 milligrams per kilogram cohort, but the endpoint
5 was met at 24 weeks for the 30 milligram per
6 kilogram cohort with an absolute change from
7 baseline and present dystrophin positive fibers of
8 13.7 percent with no increase seen in the placebo
9 group at week 24.
10 The FDA suggested that this lack of positive
11 effect at an earlier time point with higher dose
12 sheds doubt on the later time point. Our data
13 indicate, however, that duration rather than dose
14 appears to the be the critical factor for
15 dystrophin production.
16 Although in an earlier study increased
17 dystrophin was observed in some patients by
18 week 12, the response was not consistent across all
19 patients. Study 201/202 showed increased
20 dystrophin in all biopsied patients at week 24 that
21 was sustained at later time points.
22 The week 180 biopsy is considered the most

1 important because samples were evaluated using
2 methods, blinding, and controls developed in
3 consultation with FDA. However, FDA noted concerns
4 regarding the selection of the untreated controls,
5 anatomical location of controls, and blinding
6 procedures.
7 Baseline tissue was only available for
8 3 patients from study 201, therefore we obtained
9 additional samples from a highly comparable group,
10 untreated patients who were the first 6 patients
11 with available tissue from the PROMOVI confirmatory
12 study.
13 Of note, they had similar enrollment
14 criteria to study 201 and were not previously
15 analyzed for dystrophin. Collectively, this
16 provided 9 untreated controls, which represent a
17 robust internal comparator for measurement of
18 dystrophin.
19 As the FDA noted, we compare biopsies from
20 deltoid to biceps. There is no evidence to suggest
21 that dystrophin levels would differ in these
22 muscles since both are proximal upper extremity

1 muscles equally affected in DMD patients. This was
2 confirmed by our own analysis of the baseline
3 samples.
4 Finally, these assays were performed by
5 independent technicians who were blinded to sample
6 treatment status with a different sample
7 randomization used for each assay.
8 We have learned a lot about dystrophin
9 measurement in the course of the eteplirsen
10 development, and our methods have evolved
11 accordingly. Our validated Western blot method,
12 optimized to detect low levels of dystrophin, is
13 arguably the first dystrophin Western blot to be
14 truly quantitative.
15 This was achieved by use of a 5 point
16 calibration curve on each gel and prespecified
17 loading and exposure limits to avoid signal
18 saturation. Furthermore, samples were randomized,
19 blinded and run in duplicate on separate gels. In
20 contrast, the Western blot methods in the majority
21 of historical publications referenced by FDA were
22 performed using older methodology that is

1 semi-quantitative at best.
2 Given these significant methodological
3 differences, it is inappropriate to compare our
4 data to literature approximations. Instead,
5 treatment effect should be assessed by comparing
6 untreated baseline tissue to post-treatment samples
7 using the same validated assay. This enables
8 accurate determination of a fold increase in
9 dystrophin level.
10 Western blot analysis of week 180 biopsies
11 show that 9 out of 11 biopsied eteplirsen patients
12 in the 201/202 study had an obvious and
13 quantifiable dystrophin band resulting in a mean of
14 0.9 percent. The untreated samples had a mean of
15 0.08 percent.
16 Importantly, this baseline calculation is
17 based on a predefined protocol that was developed
18 in collaboration with the FDA. This represents an
19 11.6-fold increase and includes the available
20 baseline samples obtained from study 201.
21 The FDA questioned whether this robust
22 increase in dystrophin level was significant based

1 on historical approximations in the range of
2 3 percent of normal. As detailed earlier, direct
3 comparison cannot be made to literature values.
4 The only scientifically valid comparison is to
5 these untreated DMD controls.
6 Turning to our analysis of percent
7 dystrophin positive fibers, FDA questioned certain
8 important details, which I would like to clarify.
9 First, only unenhanced images were used to score
10 positive fibers. Second, an unbiased systematic
11 sampling method was used to select the fields for
12 image capture.
13 Third, a prespecified protocol was carefully
14 developed to avoid overestimation of dystrophin
15 positive fibers, with viewing conditions controlled
16 to allow optimal viewing of the original unaltered
17 images, positive fibers defined as having intensity
18 above untreated DMD fibers in at least 30 percent
19 of the membrane circumference, and a requirement
20 that each pathologist be trained and pass
21 prespecified qualifications prior to scoring.
22 The rigor of the protocol and training is

1 supported by the higher inter-rater reliability
2 that was observed for analysis of the week 180
3 images.
4 Three pathologists observed a significantly
5 higher mean percent dystrophin positive fiber count
6 and a 15.5-fold increase for eteplirsen patients in
7 comparison to untreated controls. The
8 immunohistochemistry images were also assessed for
9 fluorescence intensity by a computer algorithm.
10 As shown in this graph, a significant higher
11 mean relative fluorescence intensity and a 2.4-fold
12 increase was observed for eteplirsen patients in
13 comparison to the untreated controls.
14 As both Dr. Mercuri and I mentioned earlier,
15 DMD patients amenable to exon 44 skipping
16 experience a milder phenotype. The mean intensity
17 for eteplirsen is 22.6 percent, which is comparable
18 to the approximately 20 percent seen for exon 44
19 amenable patients.
20 In contrast to Western blot data, which
21 cannot be compared to published reports,
22 immunohistochemical intensity comparison is valid

1 when contemporary standardized methods are used.
2 Evaluating the relationship between Western
3 blot and immunohistochemical intensity shows that,
4 as expected, the normal controls are in the highest
5 values. Untreated DMD samples are the lowest and
6 week 180 treated DMD and Becker samples fall in
7 between. It is important to note that one of the
8 low expressing Becker patients overlaps with our
9 week 180 treated samples.
10 A strong correlation between these two
11 quantitative measures has been reported in several
12 independent publications. As noted by the FDA, the
13 correlation between Western blot and PDPF is not
14 strong. This is not unexpected given that PDF is a
15 semi-quantitative measure.
16 To summarize, we have clearly demonstrated
17 that sustained production of de novo dystrophin by
18 all measures employed. Biochemical evidence of
19 functionality includes correct localization of
20 dystrophin and key associated proteins to the
21 sarcolemmal membrane. Taken together, these data
22 clearly demonstrate that eteplirsen is working as

1 intended.

2 Next, I will present the clinical data that
3 demonstrate that the observed increase in
4 dystrophin results in a clinically meaningful
5 benefit. Before I do that, I would first like to
6 describe our early 48 week data and explain why it
7 suggested the need for a longer study.

8 In an exploratory analysis, we looked at the
9 first 48 weeks of study 201/202. We saw that
10 2 patients, shown in light blue, experienced rapid
11 decline before the 24-week time point and lost
12 ambulation shortly thereafter.

13 Based on what we know now, consistent
14 increase in dystrophin is not observed until
15 24 weeks suggesting that these patients declined
16 prior to dystrophin production. An analysis was
17 conducted of continuously treated patients who
18 remained ambulant, shown in dark blue, as well as
19 the placebo delayed patients who rolled onto
20 treatment at week 25, shown in gray. Both groups
21 experienced relative stability.

22 Based on these limited but encouraging

1 results, study 202 was extended. To be clear, the
2 two boys who lost ambulation remained on treatment
3 and are included in all subsequent analyses
4 presented.
5 In order to evaluate the long-term data from
6 study 201/202, FDA suggested comparison to an
7 external control group. This was accomplished by
8 pooling eteplirsen data into a single group with
9 the original placebo patients reset to time zero at
10 the initiation of the eteplirsen treatment. This
11 provides data from 12 patients for a 4-year time
12 period.
13 A key aspect to the data comparison of
14 course is the appropriateness of the external
15 control. We recognize that a key issue for
16 external controls is the potential for bias. We
17 looked carefully at the regulations and guidance,
18 and I would like to begin by addressing the key
19 issues.
20 First, bias can be due to both known and
21 unknown prognostic factors. We controlled for the
22 key prognostic factors that are known.

1 Second, the selection of the control group
2 should be made prior to the comparative analysis.
3 We used prespecified selection criteria that were
4 based on the 201 enrollment criteria.
5 Third, the disease course has to be
6 predictable. We selected a homogeneous patient
7 population with a predictable disease course.
8 Fourth, the endpoints need to be objective.
9 We used a highly standardized 6-minute walk test
10 measure.
11 Fifth, patient level data are required for
12 comparison. We had 4-year longitudinal patient
13 level data that was highly comparable on baseline
14 characteristics, including steroid use and other
15 standards of care.
16 Sixth, external controls are often perceived
17 to have worse outcomes. I will show that the
18 external control group was reflective of other
19 natural history databases.
20 And finally, and most importantly, the
21 treatment effect needs to be dramatic. You will
22 see that this was certainly the case with

1 eteplirsen.
2 In partnership with leading DMD experts,
3 Sarepta actively searched for a natural history
4 data. Twelve databases were identified having
5 extensive clinical data, however only two had
6 6-minute walk test data beyond baseline available
7 for analysis. Of note, the CINRG database did not
8 have long-term 6-minute walk test data at that
9 time.
10 The two databases identified were the
11 Italian DMD Telethon and the Leuven Neuromuscular
12 Research Center in Belgium. The studies began
13 enrolling patients in 2007/2008 and have continued
14 in a time period that is contemporary with study
15 201/202. Both databases had longitudinal 6-minute
16 walk test data available, but only the Italian
17 registry had the NSAA data available as well.
18 Importantly, all patients attending a
19 participating clinic who met eligibility criteria
20 were enrolled in the studies. Results from these
21 investigator initiated studies have been published
22 in peer review journals.

1 All centers in the studies were treating
2 patients according to the international standards
3 of care for DMD that were discussed by Dr. Mercuri.
4 FDA raised concerns about lower adherence to
5 standards of care for children in Italy, however,
6 this is of limited relevance to the actual care
7 received by our external control patients who were
8 seen at neuromuscular specialty clinics. As I will
9 later demonstrate, our external control had
10 extremely high compliance to the standards of care.
11 As is common in rare diseases, treating
12 clinicians represent a small but highly
13 collaborative international community.
14 Importantly, the 6-minute walk test was assessed by
15 the same method for eteplirsen patients and for
16 external controls.
17 Both databases as well as the eteplirsen
18 study used the modified 6-minute walk test protocol
19 adapted for use in DMD. As was described by
20 Dr. Mercuri, this included use of the same scripted
21 encouragement. In addition, the lead physical
22 therapist for the Italian registry and study

1 201/202 previously worked together on an
2 international effort to standardize the protocol
3 and training for the 6-minute walk test in DMD.
4 This ensured comparable clinical evaluations
5 between the various sites.
6 Having obtained the patient level data, we
7 next set out to find the most appropriate patients
8 for comparison. The enrollment criteria for
9 study 201/202 were used to select patients from the
10 external control group. These included steroid
11 use, age greater than or equal to 7 years, and a
12 mutation amenable to exon 51 skipping.
13 Importantly, these filters were defined before data
14 analysis began.
15 I would like to remind you that these
16 criteria were specifically designed to select for
17 boys in the decline phase of the disease.
18 Pooling the data that Sarepta received from
19 the two databases rendered a raw data set of 186
20 patients. The Italian Telethon only provided
21 patients who had been evaluated for at least 3
22 years, while the Leuven Neuromuscular Research

1 Center provided patients who had been evaluated for
2 varying lengths of time. The selection criteria
3 from 201/202, just described, were applied to these
4 patients.
5 An initial filter was applied requiring
6 steroid use at baseline as well as a minimum of
7 both a baseline and one post-baseline 6-minute walk
8 test result. A second filter was applied to
9 exclude patients younger than 7 who were likely to
10 be improving in the 6-minute walk test due to
11 growth and maturation.
12 Since mutation type impacts disease
13 severity, filters were applied to find patients
14 amenable to skipping any exon, and finally amenable
15 only to exon 51 skipping. Efficacy results will
16 compare eteplirsen patients to this primary
17 analysis group.
18 In addition, a secondary more conservative
19 comparison to a larger population of 50 patients
20 amenable to any exon skipping included milder
21 exon 44 patients was presented in our briefing
22 document.

1 A critical question is how comparable this
2 external control group is to the eteplirsen group.
3 We see here that the eteplirsen cohort on the left
4 is highly comparable on key prognostic factors to
5 the primary external control group on the right.
6 Looking first at the mean baseline age, we see that
7 the groups are very similar.
8 Mean baseline 6-minute walk test values are
9 also highly comparable with the groups differing by
10 less than 10 meters. Of note, all deletion
11 mutations observed among the 12 eteplirsen boys are
12 also represented in the external control.
13 As Dr. Mercuri detailed, steroid use has
14 been shown to impact disease progression.
15 Importantly, the eteplirsen patients as well as all
16 external controls were on a stable dose of steroids
17 at least 6 months prior to enrollment and remained
18 on steroids throughout the study.
19 The two most commonly described steroids in
20 DMD, deflazacort and prednisone, were used in equal
21 proportion by both groups. Of note, the majority
22 of patients in the external control actually

1 maintained a higher dose than the eteplirsen
2 patients.
3 As FDA noted, there are two minor
4 differences in steroid treatment between the
5 external control and eteplirsen, neither of which
6 significantly impacted the 6-minute walk endpoint.
7 First, the mean age of steroid initiation
8 for external control is approximately 1 year older
9 than eteplirsen. This difference is partly
10 attributed to a single external control patient who
11 began steroid use at age 10.7 years. Of note, he
12 had a better prognosis and maintained ambulation
13 until he was over 15.
14 Second, a lower percentage of eteplirsen
15 boys received an intermittent steroid regimen in
16 comparison to external control. Sensitivity
17 analyses for both of these variables demonstrate
18 minimal impact on the primary endpoint.
19 In addition, we plotted the change in
20 6-minute walk test by steroid regimen for the
21 external control. The intermittent patients shown
22 in orange experienced similar declines as the

1 continuous patients shown in green. Taken
2 together, with a sensitivity analysis, this
3 suggests that steroid dosing frequency did not
4 affect the results of the 6-minute walk test in our
5 analysis.
6 Physical therapy and use of orthoses can
7 also impact ambulation. As shown here, the
8 external control patients received a higher level
9 of physical therapy intervention with all 13
10 meeting with a physical therapist at least twice a
11 week.
12 Additionally, there was a high compliance
13 with the use of night splints. This demonstrates
14 that the external control patients had high
15 adherence to standards of care. This is not
16 surprising since they were treated in leading
17 neuromuscular centers.
18 In addition to looking at comparability of
19 baseline characteristic, it is important to address
20 concerns regarding the potential for motivational
21 bias in the external control. FDA had performed an
22 alternative comparison for eteplirsen based on the

1 drisapersen placebo data.
2 To test for the potential motivation bias,
3 we did an analysis comparing the 6-minute walk test
4 results for our external control group to this
5 data. Patients in the drisapersen study were also
6 amenable to exon skipping and on steroids.
7 However, they included patients younger than 7 who,
8 as Dr. Mercuri noted, would be expected to improve
9 over time.
10 These drisapersen patients were initially on
11 placebo, shown in dashed black, and then rolled
12 over onto treatment, shown in solid black.
13 Motivation does not appear to be a factor given
14 that our external control, shown in yellow,
15 experienced similar declines to patients in the
16 drisapersen trial.
17 I would now like to clarify a few
18 misunderstandings regarding our key data and then
19 review the clinical results. As it relates to the
20 external control, FDA raised three key issues.
21 First, there was a concern that revisions
22 occurred to the external control data regarding

1 continuous versus intermittent steroid use. To
2 clarify, 3 patients with unknown regimens at the
3 time of NDA submission were later reported by the
4 investigator as receiving a continuous regimen.
5 Second, the FDA stated that 2 patients left
6 to enter interventional trials, leading to
7 potential difference between eteplirsen and
8 external control patients. In fact, we acquired
9 the missing 6-minute walk test data for these two
10 patients after they participated in the placebo arm
11 of an interventional study and have included their
12 6-minute walk test results in the analyses.
13 Third, as Dr. Mercuri noted, it is common
14 for patients to have a 6-minute walk test of zero
15 while still being able to perform the 10-meter walk
16 run.
17 In addition, FDA raised two key concerns in
18 the approach to Sarepta's analysis of the 6-minute
19 walk test and the North Star ambulatory assessment.
20 First, they noted that eteplirsen patients had two
21 opportunities to perform a functional test whereas
22 natural history patients had only one. To be

1 clear, day 1 values for the 6-minute walk test and
2 all other measures were compared to single external
3 control measurement.
4 Finally, we would like to clarify that while
5 FDA identified 2 external control patients as
6 having missing North Star ambulatory assessment
7 values, we correctly incorporated these values into
8 our analysis and did not assign them values of
9 zero. You can see that we have carefully reviewed
10 the data, and we will be happy to address any other
11 questions.
12 Comparison to the external control to
13 eteplirsen was conducted over 3 to 4 years. Four
14 years of data were analyzed for 6-minute walk test
15 and loss of ambulation, while 3 years of data were
16 analyzed for the North Star ambulatory assessment
17 and ability to rise. These time periods were based
18 on the availability of external control data.
19 As I review the results, keep in mind that
20 the treatment expectation for eteplirsen is to
21 delay but not necessarily to stop disease
22 progression. Any preservation of ambulation, even

1 by a couple of years, would significantly impact
2 the lives of patients and their families.
3 Our primary analysis is comparison of the
4 external control group to eteplirsen patients on
5 change in the 6-minute walk test. In this
6 analysis, any patient who lost ambulation
7 contributed a score of zero to the mean.
8 As you can see the two groups had highly
9 comparable 6-minute walk test values at baseline
10 and year 1, confirming their similarity. We did
11 not expect an immediate separation between treated
12 and untreated patients because, first, an increase
13 in dystrophin expression is not observed until
14 24 weeks. And second, time is required for the
15 untreated control group to decline.
16 After year 1, the groups diverge, and by
17 years 3 and 4, we see a nominally significant
18 difference of 148 and 162 meters, demonstrating
19 that eteplirsen slowed disease progression. This
20 large magnitude of effect is equal to the length of
21 nearly two football fields.
22 In this graph, individual 6-minute walk test

1 results are shown in yellow for the exon 51
2 external controls. These patients experienced
3 declines in 6-minute walk test over 4 years, and 10
4 lost ambulation by year 4, as indicated by a
5 6-minute walk test score of zero.
6 In comparison, the eteplirsen group, shown
7 in blue, declined more slowly after year 1. No
8 additional patients lost ambulation after year 1.
9 As you can see, the difference is not driven by a
10 few patients who performed particularly well or a
11 few external control patients who performed
12 particularly poorly.
13 For our analysis, loss of functional
14 ambulation is defined as the inability to execute
15 the 6-minute walk test. This bar graph shows the
16 estimated loss of ambulation at annual time points
17 based on Kaplan-Meier analysis. Two external
18 control patients had missing data, and Kaplan-Meier
19 analysis properly accounts for this.
20 The cumulative loss of ambulation over the
21 first 4 years remain constant at 17 percent for
22 eteplirsen patients. In contrast, a continual

1 increase in loss of ambulation is observed in the
2 external control patients culminating in an
3 85 percent probability of losing ambulation by
4 year 4.
5 FDA presented the loss of ambulation by age.
6 The analysis shown here is from the CINRG database,
7 a global, multicenter study of DMD. These are
8 steroid treated patients amenable to exon 51
9 skipping similar to eteplirsen and external control
10 patients, however, there are two important
11 differences when comparing the CINRG data to
12 eteplirsen.
13 First, the definition of loss of ambulation
14 for CINRG was full wheelchair use and was confirmed
15 by inability to perform the 10-meter walk/run when
16 possible. This is critically different from our
17 definition, which was zero on the 6-minute walk
18 test.
19 As mentioned earlier, it is not unusual to
20 see a zero on the 6-minute walk test and still have
21 a positive value on the 10-meter walk/run. Because
22 of these different definitions, the CINRG database

1 is more likely to report a later loss of ambulation
2 in some patients. Despite this, our external
3 control, shown in dashed yellow, performed somewhat
4 better than these CINRG patients.
5 The eteplirsen patients shown in blue appear
6 to behave differently than either the CINRG or the
7 external control groups. Of note, the eligibility
8 criteria used for eteplirsen has an upper limit of
9 440 meters on baseline 6-minute walk test, which
10 precludes milder patients who are likely to walk
11 longer. However, these milder patients were not
12 excluded from the CINRG database.
13 FDA focuses on the outliers from the CINRG
14 database to suggest DMD patients maintain
15 ambulation into their late teens, concluding that
16 eteplirsen boys do not differ from the natural
17 history. Of note in the CINRG database, there are
18 only 3 boys who are walking past the age of 15.
19 The more appropriate comparison is the
20 median loss of ambulation between these three
21 groups. The median ages of loss of ambulation are
22 12 for CINRG, 12.9 for the external control, and

1 the median loss of ambulation has not yet been
2 reached for eteplirsen boys. Most importantly,
3 eteplirsen preserves ambulation longer than either
4 the CINRG database or the external control.
5 We are fortunate to have Dr. Craig McDonald,
6 the chair of the CINRG study, available today to
7 answer questions regarding the database and loss of
8 ambulation in DMD.
9 In addition to ambulatory ability, a number
10 of supportive endpoints were also evaluated.
11 Comparison to external control for these endpoints
12 is shown through year 3. Similar to the 6-minute
13 walk test results, the North Star ambulatory
14 assessment shows a slower decline in the treated
15 group at 2 and 3 years following the same trend as
16 the 6-minute walk test. While the observed
17 difference of 2.4 points on the North Star
18 ambulatory assessment is not significant, it
19 represents the critical preservation of one or more
20 activities of daily living.
21 Here we show the ability to independently
22 rise from supine for external controls compared to

1 eteplirsen patients. Ability to rise is a more
2 standardized definition since in contrast to rise
3 time, it does not allow for external support.
4 Consistent with the 6-minute walk test results, the
5 two groups are initially comparable and then
6 diverge.
7 By year 3, more than half of the eteplirsen
8 patients could still rise from the floor
9 independently compared to only 8 percent of
10 external control, a difference that is nominally
11 significant.
12 In summary, it is our position that the data
13 you have seen confirm eteplirsen's mechanism of
14 action and demonstrate that eteplirsen slows
15 disease progression. Eteplirsen is the first
16 therapeutic to unequivocally demonstrate an
17 increase in dystrophin following treatment.
18 The external control is a highly comparable
19 and appropriate comparator to evaluate eteplirsen's
20 clinical effect. Analysis of drisapersen placebo
21 and CINRG data confirm that our external control is
22 representative of natural history.

1 Eteplirsen slowed disease progression,
2 demonstrating a clinically meaningful effect on the
3 6-minute walk test and a dramatic difference in
4 loss of ambulation. Eteplirsen benefit is further
5 supported by the North Star ambulatory assessment
6 and ability to rise from supine.
7 While we demonstrated clinical benefit in
8 our initial studies, because we are seeking
9 accelerated approval, confirmatory studies are
10 required for full approval. When we had to make
11 the critical decision of how to further evaluate
12 eteplirsen, we determined that a placebo-controlled
13 trial would not be feasible because there were not
14 enough eligible exon 51 amenable patients due to
15 other ongoing trials. In addition, the patient
16 community expressed opposition to a long-term
17 placebo-controlled eteplirsen study.
18 Therefore, in consultation with FDA, a
19 flexible approach was adopted using non-exon 51
20 amenable patients to a comparator arm. This
21 approach incorporated what we learned, including
22 the need for a longer study duration and updated

1 enrollment criteria to exclude rapidly progressing
2 boys such as the two who lost ambulation in
3 study 201.
4 The first confirmatory study is an
5 open-label comparison of exon 51 patients treated
6 with eteplirsen to untreated DMD patients who are
7 amenable to skipping other exons but who would not
8 benefit from eteplirsen.
9 The second study is a double blind,
10 placebo-controlled trial of two follow-on drugs.
11 Both have the same PMO backbone as eteplirsen and
12 utilize the same mechanism of action, but rather
13 than skipping exon 51 these drugs skip exons 45 and
14 53, respectively.
15 To provide further detail, the first
16 confirmatory study, PROMOVI, is a 96-week
17 open-label, multicenter study comparing 60
18 eteplirsen patients to 60 untreated, non-exon 51
19 amenable boys having the same entry criteria.
20 These criteria are similar to study 201/202
21 but with updated 6-minute walk test cutoffs to
22 exclude patients likely to decline before

1 dystrophin can be produced. This study is already
2 underway, but a data readout is not expected for at
3 least another 2 to 3 years.
4 The second study, ESSENCE, is a 96-week
5 randomized, double-blind, placebo-controlled
6 multicenter study of our next two drugs, which
7 treat patients amenable to skipping exon 45 and 53,
8 respectively.
9 Recall from Dr. Mercuri's presentation that
10 patients amenable to skipping exon 45 or 53
11 experienced a similar rate of decline on the
12 6-minute walk test as patients amenable to skipping
13 exon 51. This will be a 99-patient study with a
14 2 to 1 randomization of drug to placebo with entry
15 criteria matching PROMOVI. Enrollment is expected
16 soon.
17 I would now like to introduce Dr. Eliopoulos
18 who will review the safety data.
19 **Applicant Presentation - Helen Eliopoulos**
20 DR. ELIOPOULOS: Thank you, Dr. Kaye.
21 Good morning. Following a brief description
22 of non-clinical data, I will present the integrated

1 analysis of safety, including adverse events that
2 were common, serious or severe, resulted in
3 discontinuation, or were of special interest.
4 Eteplirsen is a PMO structurally and
5 biologically distinct from other RNA analogues. In
6 non-clinical studies of eteplirsen, the kidney was
7 identified as the organ of toxicity. In contrast
8 to other RNA analogues, including one recently
9 reviewed by this committee, toxicities such as
10 immune activation, thrombocytopenia, coagulopathy,
11 or vasculitis were not seen with eteplirsen.
12 The integrated safety analysis includes 114
13 DMD patients from 7 studies, all patients with
14 mutations specifically amenable to exon 51
15 skipping. Twenty-six patients received lower
16 eteplirsen doses and were from study 33, which
17 administered a single IM dose or study 28,
18 dose ranging for IV eteplirsen.
19 Eighty-eight boys received the proposed dose
20 of 30 milligrams per kilogram or higher, including
21 12 boys from pivotal studies 201/202, who have
22 received eteplirsen for about 4 years. Younger

1 patients, age 4 to 6 from study 203, as well as
2 patients with more advanced DMD from study 204,
3 have contributed to the integrated set.
4 This table lists common adverse events
5 occurring in 10 percent or more of the 114
6 patients. The majority of events were mild and
7 transient, resolving with continued eteplirsen.
8 And as you could see, many of these could be
9 anticipated in a pediatric population with
10 Duchenne.
11 Only 2 of 114 patients had serious adverse
12 events, but neither of these appear drug related.
13 One patient, an 11-year-old boy, had a femur
14 fracture after falling out of his wheelchair. He
15 had previous events of severe but non-serious
16 balance disorder and bone pain. And the second, a
17 9-year-old boy, had post-operative vomiting after
18 general anesthesia. Of note, there have been no
19 fatal or life-threatening events with eteplirsen.
20 Out of 114 patients, there was only 1 who
21 discontinued eteplirsen due to adverse events, and
22 this was a 10-year-old boy who was reported to have

1 cardiomyopathy after 7 weeks of a low dose of
2 eteplirsen at 4 milligrams per kilogram. This was
3 based on an observed decrease of left ventricular
4 fractional shortening on echo. The investigator
5 considered this as severe and possibly related to
6 drug.
7 To further evaluate, Sarepta undertook an
8 independent cardiology review, which interpreted
9 the echo findings as normal and considered that
10 changes in fractional shortening were possibly due
11 to technical factors.
12 There was one additional case of
13 cardiomyopathy in the integrated set, not leading
14 to study drug discontinuation, in a patient with
15 preexisting history. Overall, these two reports
16 represent a rate of about 2 percent consistent with
17 the known prevalence of cardiomyopathy in DMD.
18 Severe events were experienced by three
19 additional patients. A 7-year-old boy experienced
20 bleeding from a Portacath incision site after
21 swimming. Coagulation parameters were normal at
22 the time of the event.

1 In two other patients, events of nasal
2 congestion, hemorrhoids, and back pain due to a
3 fall were reported, and again, these appeared
4 consistent with events that may occur in a
5 pediatric DMD population.
6 Adverse events of special interest were
7 based on the non-clinical findings for eteplirsen
8 as well as events of interest from the clinical
9 experience with other RNA analogues.
10 As non-clinical studies identified the
11 potential for kidney toxicity, a broad review of
12 renal events was conducted. There were 11 patients
13 with proteinuria described as protein detected by
14 dipstick based on urinalysis. All events were mild
15 and transient. There was one patient with adverse
16 events of increased BUN and creatinine in the
17 setting of dehydration occurring at week 88 of
18 eteplirsen. These resolved by the time of retest
19 11 days later and have not recurred with continued
20 eteplirsen for a period of over 2 years.
21 As immunogenicity has been an issue for
22 other RNA analogues, potential infusion reactions

1 have been reviewed. A subset of 107 patients have
2 received IV eteplirsen, representing over 3900
3 infusions. Twenty-two percent of these patients
4 experienced an infusion site event, this table
5 listing those occurring in 2 or more patients.
6 Most events were described as catheter or
7 infusion site pain or hematoma consistent with
8 placement of a catheter device. Of note, there
9 were 4 events of mild pyrexia considered unrelated
10 to drug. An additional report of mild temperature
11 elevation occurred coincident with an eteplirsen
12 infusion and is therefore considered a potential
13 adverse drug reaction. There have been no serious
14 or severe infusion site reactions with eteplirsen.
15 In the all-eteplirsen group, 24 percent of
16 patients had events, which were assessed for
17 potential hyper-sensitivity. All events were
18 non-serious and resolved. The majority, including
19 rash and pruritus, were mild and considered
20 unrelated to study treatment by nature of the
21 temporal relationship or lack of recurrence with
22 ongoing treatment.

1 Two types of events, mild erythema, and
2 flushing, occurred during eteplirsen infusions.
3 They were considered related by the investigators
4 and represent potential mild adverse drug
5 reactions. There have been no serious or severe
6 events related to hypersensitivity with eteplirsen.
7 Review of the safety database and
8 longitudinal laboratory data identified no
9 clinically significant events for thrombocytopenia,
10 coagulopathy, vasculitis, immune-mediated
11 disorders, or hepatic toxicity, consistent with the
12 absence of such findings in non-clinical studies of
13 eteplirsen.
14 In summary, characterization of the
15 eteplirsen safety profile is early, however, no
16 significant safety risks have been identified. The
17 majority of reported adverse events have been mild
18 and resolved with continued therapy, suggesting
19 they were not drug related.
20 Favorable tolerability is demonstrated by
21 the low rate of discontinuations and serious
22 events. Sarepta continues to evaluate the safety

1 of eteplirsen through monitoring of ongoing trials,
2 as well as planned post-marketing surveillance and
3 a DMD registry.
4 I would now like to introduce Dr. Mendell,
5 the principle investigator for study 201/202, who
6 will provide the clinical perspective for
7 eteplirsen in the treatment of boys with DMD.
8 **Applicant Presentation - Jerry Mendell**
9 DR. MENDELL: My name is Dr. Jerry Mendell,
10 and I currently serve as director of the Center for
11 Gene Therapy at Nationwide Children's Hospital.
12 I'm uniquely positioned to provide a clinical
13 perspective as the PI for the eteplirsen 201 and
14 202 studies since 2011. I'm a paid consultant for
15 Sarepta in preparation for today, but I stand to
16 gain no financial benefit from FDA approval of
17 eteplirsen.
18 My experience in the management and care of
19 DMD boys extends back to my post-doctoral position
20 at NIH in 1969. When I started caring for DMD boys
21 at that time, there were no treatments, and I made
22 a personal commitment that over my lifetime, I

1 would make a difference for boys with this
2 devastating disease.
3 There are three elements that emphasize the
4 foundation for eteplirsen approval for the
5 treatment of DMD. I refer to these as the
6 treatment triad.
7 The first leg of the triad is prolonged
8 ambulation. To be clear, the FDA is suggesting
9 that boys with DMD are able to walk until the age
10 of 16. This is not my experience, nor is it
11 reflected in the data from CINRG, which shows loss
12 of ambulation at a median age of 12 in exon 51
13 amenable patients. In the eteplirsen study,
14 10 boys are still walking 4 years after starting
15 therapy. Their median age is 13.4, and the median
16 age of loss of ambulation has not been reached for
17 this cohort.
18 Why is this important? Simply put, the
19 complications of wheelchair dependency have a major
20 cascading effect that is both physical, including
21 scoliosis and osteoporosis, and emotional, a change
22 in body image leading to a loss of self-esteem. In

1 addition, many of the rapidly advancing
2 translational treatments are denied to
3 wheelchair-dependent patients.
4 The second leg of the triad is the safety
5 profile of eteplirsen. I have done many clinical
6 trials over the past 40 plus years, and I have
7 never seen tolerability like we have seen in this
8 trial. There has not been a single serious adverse
9 event related to treatment in over 3900 infusions
10 of eteplirsen.
11 The third leg is what I refer to as the
12 consistency profile of eteplirsen treatment. This
13 is best illustrated by the maintenance of
14 ambulation after 4 years of therapy.
15 Dr. Kaye presented an exploratory analysis
16 excluding the two boys who lost ambulation early in
17 the study. Here we see the mean change from
18 baseline through week 216. For clarity, we have
19 shown both treatment groups starting at the zero
20 point.
21 What interests me is what happens after
22 week 48. Here we see a long-term stabilization and

1 a consistent parallel course between both groups,
2 however the placebo delayed treatment group never
3 catches up, sending a clear message that there is a
4 treatment effect of eteplirsen. The consistency of
5 the data is remarkable giving the protocol mandates
6 that the distance measured for each patient be
7 recorded and transcribed in the case report forms
8 without looking back at the previous result.
9 I'd also like you to know that what we have
10 observed in the eteplirsen treated patients is very
11 different from what I have seen in the natural
12 history. I know this because every DMD boy who
13 comes to Nationwide Children's Hospital for ongoing
14 care undergoes a 6-minute walk test with the same
15 physical therapist, under the same condition as the
16 eteplirsen trial, and we simply don't see similar
17 results.
18 This graph also emphasizes that there are no
19 claims that eteplirsen is a cure for DMD.
20 Eteplirsen slows progression, which results in
21 maintained ambulation.
22 The next slide allows us to look again at

1 loss of ambulation over 4 years. In the exon 51
2 external control matched for age and mutation, the
3 risk of loss of ambulation is 85 percent for
4 external control patients compared to 17 percent
5 for eteplirsen.
6 As previously stated, a major goal of this
7 trial was to delay the loss of ambulation. Our
8 data suggests that the unequivocal increase in
9 dystrophin by eteplirsen cannot be ignored as an
10 explanation for prolonged ambulation. Preserving
11 walking is key to maintaining physical and
12 emotional wellbeing.
13 The numbers are one thing, but my personal
14 enthusiasm for these findings is best demonstrated
15 by the quality of walking in eteplirsen treated
16 patients, as we see on the next slide.
17 This is Billy in the red cap. He's now 15,
18 and he's one of my patients in the eteplirsen
19 trial. Here he's walking in the last mile of the
20 Pittsburgh marathon. First of all, boys at this
21 age with DMD usually don't walk, and they certainly
22 don't walk in the last leg of a marathon. But here

1 he is, and I want you to watch closely because not
2 only does he walk, but he has gained enough self-
3 esteem to attempt jogging as if to emulate other
4 participants in this highly competitive trial. Go
5 Billy.
6 (Applause.)
7 This quality of ambulation at 15 just
8 doesn't happen in DMD.
9 In summary, I see treatment of DMD as a race
10 against time. If you shadowed me in clinic, you
11 would find that most boys at age 14 are in a
12 wheelchair. Fifteen-year-old boys like Billy don't
13 maintain ambulation by accident. This is a very
14 gratifying result for a long-term clinician.
15 Eteplirsen offers a genuine opportunity to
16 change the natural history of this disease by
17 slowing progression and improving quality of life.
18 I can't see any grounds for withholding this drug
19 for DMD boys. The opportunity before the panel is
20 to give the DMD boys in my clinic, and in other
21 clinics, the same chance as we observed in the
22 eteplirsen trial.

1 I want to thank this panel of reviewers, the
2 team of researchers at Nationwide Children's
3 Hospital, and the collaborators at multiple sites
4 for helping to make this happen. Most of all, I
5 want to thank the 12 heroic boys and their families
6 who selflessly dedicated themselves to this
7 groundbreaking research. And finally, I want to
8 turn this podium back over to Dr. Kaye for
9 concluding remarks.
10 (Applause.)
11 **Applicant Presentation - Edward Kaye**
12 DR. KAYE: Today the FDA has presented to
13 you a number of important questions for your
14 consideration. To help you in your deliberations,
15 allow me to conclude by reviewing three of the most
16 critical and then offer Sarepta's position on each.
17 The first question focuses on the provision
18 of adequate evidence. The agency has asked if
19 eteplirsen produces dystrophin to a level that is
20 reasonably likely to predict clinical benefit.
21 Today we presented data that shows an unequivocal
22 increase in functional de novo dystrophin by three

1 complementary methods. Most important, we shared
2 with you the fact that even small amounts of
3 dystrophin are known to confer clinical benefit.
4 The second question focuses on the 6-minute
5 walk test. It asks if the test is sufficiently
6 objective and free of bias to allow for a valid
7 comparison. Sarepta's position is clear. The
8 6-minute walk test is both standardized and
9 considered highly reliable. Moreover, our external
10 control results are consistent with other natural
11 history databases.
12 The third and final question focuses on
13 whether our clinical studies have provided
14 substantial evidence that eteplirsen is effective
15 for the treatment of DMD. Once again, our answer
16 is yes. The data set we've presented to you shows
17 a dramatic positive effect on the 6-minute walk
18 test as well as on the loss of ambulation for over
19 4 years.
20 All of us here today agree that bringing new
21 and effective therapies to boys suffering from DMD
22 is both critical and urgent. But we also know that

1 in the field of rare diseases large
2 placebo-controlled studies present significant
3 challenges.
4 As Ms. Ruff said in her opening remarks,
5 given the limitations of our database, we both
6 understand and appreciate the difficulty of your
7 decision today, yet we believe it is both
8 reasonable and prudent to approve eteplirsen based
9 on the totality of the data we have presented
10 today.
11 Let me conclude our formal presentation with
12 this. Sarepta stands ready to work with the entire
13 DMD community, patients, caregivers, providers, and
14 our colleagues at the FDA to continue our
15 groundbreaking work and hasten the day when we can
16 say with certainty we have a cure.
17 I would now like to introduce Christine
18 McSherry from the Jett Foundation.
19 (Applause.)
20 **Applicant Guest Speaker Presentation**
21 **Christine McSherry**
22 MS. McSHERRY: Thank you, Dr. Kaye, and to

1 Sarepta for donating some of your time today for
2 our presentation. I am Christine McSherry, a
3 registered nurse, the executive director at Jett
4 Foundation, but most importantly a mom of a
5 20-year-old with Duchenne.
6 My son, Jett, is enrolled in study 204,
7 Sarepta's safety study for the advanced patient
8 population, and he's been receiving eteplirsen for
9 18 months. Jett took his last step when he was 13.
10 I started the Foundation in 2001 with a
11 mission to improve the lives of those affected by
12 Duchenne. The Foundation does not have any
13 financial interest in the outcome of this meeting,
14 and has not been compensated for this project.
15 As you heard from the sponsor's
16 presentation, FDASIA gives patients a voice in the
17 drug development process. With this law in mind,
18 we met with CDER officials many times over the last
19 4 years.
20 It was never our intent for the results of
21 the videos to be part of this outcome. It was
22 simply intended to bring context and perspective to

1 FDA on outcomes that are meaningful to patients.
2 In the spring of 2012, prior to the release
3 of public data, we heard stories about boys doing
4 well on eteplirsen. There were small but
5 meaningful things that they had never done prior to
6 taking the drug, like opening bottles of water and
7 bags of chips. Boys with Duchenne often struggle
8 with these types of activities.
9 In April 2013, we met with CDER to discuss
10 the patient experiences that we heard about and
11 they asked us for video evidence. In June, we
12 returned and presented videos of boys who were
13 jumping into pools, walking their dog, and
14 participating in sports.
15 CDER officials asked us to quantify outcomes
16 important to patients, so as requested, in July of
17 2015, we presented and submitted data on activities
18 of daily living, or ADLs, to FDA. At this meeting,
19 they indicated these results would be included in
20 the review of the eteplirsen NDA.
21 We collected this information through
22 semi-structured videotaped interviews that included

1 rating scales. Many themes emerged in this data,
2 but due to our limited time today, I'll only be
3 sharing 4 key findings: spontaneous falls, walking
4 after fractures, fatigue, and ADLs.
5 Through social media requests, 8 of the 12
6 participants in study 202 agreed to be interviewed.
7 All of these boys were over the age of 7 and in the
8 decline phase of ambulation. And importantly, we
9 interviewed the 3 largest decliners in the study,
10 including the 2 patients who lost ambulation early
11 and a boy who broke his tibia.
12 These interviews took place after the boys
13 had been receiving therapy for 3 years. We also
14 interviewed 3 boys from study 204. In total, 11
15 boys participated.
16 Our research led to several key findings,
17 all things that we would never expect to see in the
18 normal progression of Duchenne. The first finding
19 was a decrease in spontaneous falls. Now, let's
20 take a look at a video of what a typical fall looks
21 like for a child with Duchenne. This video was
22 taken during a 6-minute walk test.

1 Now, watch carefully. We've all tripped.
2 This boy doesn't trip. As you're watching, look at
3 his feet very carefully. He doesn't trip. His
4 quads just give out, giving him no time or warning
5 to brace his fall.
6 (Video played.)
7 MS. McSHERRY: That is a Duchenne fall. In
8 this instance, the physical therapist is there to
9 pick the boy up off the floor. By the age of 9,
10 the majority of boys with Duchenne are losing the
11 ability to get off the floor themselves. So if
12 this happens when no one is around, the only
13 alternative is to lie and wait until someone comes
14 to find him. Boys of this age are typically
15 gaining independence. In contrast, these boys can
16 no longer be left alone.
17 Now, let's listen to how one boy describes
18 his experience falling prior to taking eteplirsen
19 and then after he's been on therapy.
20 (Video played.)
21 MS. McSHERRY: "I don't even remember when I
22 collapsed the last time." Daily diary, spontaneous

1 falls. So the mother of this patient kept a daily
2 diary of his spontaneous falls. The Y-axis
3 represents the number of spontaneous falls per day,
4 while the X-axis represents time. This boy started
5 on drug in November of 2014, and he was falling
6 twice a day, and the falls decreased until March of
7 2015 when his falls stopped. And without the fear
8 of falling, he's able to play soccer, his favorite
9 activity, for an extended period of time.
10 We asked caregivers to report the number of
11 daily falls from the beginning of the trial to the
12 time of our interview. The bars on the X-axis
13 represent the patients from study 202 at baseline
14 and 3 years later. The Y-axis represents the
15 number of falls they experienced at those two time
16 points.
17 The gray bars in the red circle represent
18 the boys, 2 boys, who lost ambulation early in the
19 trial, and as you can see, they experienced over
20 4 spontaneous falls a day prior to losing
21 ambulation.
22 The red arrows highlight 4 boys who had been

1 falling anywhere between 5 times a day to twice a
2 week. The yellow bars reveal that over time, they
3 all essentially stopped collapsing. And
4 surprisingly, the red arrows signify that no
5 ambulatory boy is falling 3 years after starting
6 drug. This just doesn't happen with boys who have
7 Duchenne at this stage in their disease.
8 Walking after fracture, key finding
9 number 2. Spontaneous falls are also devastating
10 because they can lead to fractures, which typically
11 marks the end of our sons' walking. Families
12 affected by Duchenne have the same fear that you
13 would have of an elderly parent falling and
14 breaking a hip.
15 During our interviews, a highly experienced
16 physical therapist, who specializes in Duchenne,
17 told us, quote, "If you're 10, 11, or 12 and you
18 break a leg, I'm shocked if you would ever walk
19 again. I would say 9 times out of 10, that's the
20 end of your walking."
21 Boys with Duchenne are at high risk of a
22 fracture due to corticosteroid use. We learned

1 that 4 boys on eteplirsen had fractures, yet all 4
2 regained the ability to walk. For boys their age,
3 it's not what we would expect. We would expect
4 them to never walk again.
5 Key finding number 3, Duchenne related
6 fatigue. It's important to understand this
7 distinction. Because of Duchenne, these boys reach
8 the point of exhaustion much faster. As the
9 disease advances, they often can't make it through
10 a full day of school. They crash, sleeping for
11 hours.
12 However 5 of the 8 boys taking eteplirsen
13 either decreased or maintained their level of
14 fatigue. This is not what we would expect over
15 3 years. The other 3 boys were the ones who either
16 lost ambulation or experienced a fracture.
17 As I said before, I'm a mom of a 20-year-old
18 boy with Duchenne. And as the disease progresses,
19 these boys are completely exhausted and lose the
20 ability to do everyday things. The simple task,
21 such as lifting a spoon to their mouth, feels like
22 they're lifting heavy weights for them. And simple

1 tasks, like scratching your nose or turning over in
2 bed, become impossible.
3 Earlier in the disease when boys tire, it
4 leads them to use a wheelchair more often. Let's
5 listen to one boy's experience after being on
6 eteplirsen.
7 (Video played.)
8 MS. McSHERRY: Maintaining the ability to
9 walk, something we take for granted, but this boy
10 is able to walk with his friends. He can walk his
11 dog, and he can play like a normal kid.
12 The loss of ambulation changes every aspect
13 of normal daily living, from accessing a friend's
14 house, to taking family vacations, to home
15 modifications. It's just endless. Remember,
16 ambulation isn't just about walking. It also
17 benefits bone health, prevents scoliosis, and
18 supports breathing. It touches not just the boy,
19 but everyone else.
20 For the boy that we just heard from, the
21 6-minute walk test tells a story, but not the whole
22 story. For example, while this boy's 6-minute walk

1 test remains stable, it didn't capture the
2 improvements that we saw. He stopped falling, and
3 his fatigue was reduced. Just looking at the
4 6-minute walk test you wouldn't see the
5 improvements in these other important outcome
6 measures.
7 Key finding number 4, participating in life
8 for ADLs. Typically, when boys lose ambulation,
9 they quickly lose upper arm strength. And we fully
10 understand that eteplirsen is not a cure, and it
11 only slows the progression of the disease. So it
12 was important for us to see if the drug was having
13 a benefit in the non-ambulatory boys.
14 For this reason, we looked at the twin boys
15 who lost ambulation. We assessed 8 activities of
16 daily living that don't involve walking, such as
17 using a computer, feeding oneself, brushing teeth,
18 and using a cell phone. Despite coming off their
19 feet, both boys have maintained the ability to do
20 these activities over the 3-year time frame. This
21 would suggest a benefit in the non-ambulant
22 population.

1 The collective experience tells us that
2 eteplirsen is having a real and concrete impact on
3 the rate of disease progression. For the boys that
4 we interviewed, who were all between the ages of 10
5 and 13 and on drug for over 3 years, we saw a
6 decrease in spontaneous falls, the ability to walk
7 after a fracture, and the stabilization or
8 improvement in fatigue, and the maintenance of ADLs
9 in the non-ambulatory boys. In the time that it
10 will take to complete the confirmatory study, many
11 boys in our community will either lose the ability
12 to walk, to lift their arms, or to breathe.
13 Just two short weeks ago, Dr. Janet Woodcock
14 spoke at a breakthrough therapy briefing on Capitol
15 Hill by Friends of Cancer Research. She spoke
16 about type 1 errors, false positives, and type 2
17 errors, false negatives.
18 In the context of FDA, a type 1 error would
19 be risk of approving drugs that are unsafe or
20 ineffective, whereas a type 2 error is not
21 approving a drug that is safe and effective. She
22 said that type 2 errors are not talked about enough

1 and there needs to be a balance between the risk of
2 committing a type 1 versus a type 2 error.
3 This afternoon when you hear the human side
4 of this story, from those who have benefited from
5 this drug as well as others waiting for treatment,
6 I hope you keep in mind type 2 errors and recognize
7 that there is a very real human cost to making a
8 conclusion that a drug doesn't work when it really
9 does. Thank you.
10 (Applause.)
11 DR. ALEXANDER: Thank you. Thank you for
12 the presentation.
13 (Applause.)
14 **Clarifying Questions**
15 DR. ALEXANDER: Thank you very much. If
16 everyone could please take their seats.
17 Thank you. We'll now proceed with
18 clarifying questions to Sarepta Therapeutics. Are
19 there any clarifying questions? Please remember
20 that all participants from the panel, FDA, and
21 Sarepta should state their name for the record
22 before you speak. If you can, please direct

1 questions to a specific presenter.
2 Dr. Hoffman?
3 DR. HOFFMAN: Richard Hoffman. Eteplirsen
4 looks to be a very promising disease-modifying
5 agent, and I was wondering if the sponsor had any
6 plans to do a larger study in younger boys and at a
7 much higher dose. Thank you.
8 MS. RUFF: I'd like to ask Dr. Kaye to come
9 to the podium.
10 DR. KAYE: So the answer to your first
11 question is, yes, we have a large 60-treated
12 patient open-label study that is ongoing, and we
13 have another study in our -- which will be a
14 double-blind, placebo-controlled study, that will
15 be 99 patients in the 2 to 1 randomization for the
16 next two drugs. So that was the way of being able
17 to do a double-blind, placebo-controlled.
18 Our dose that we had determined is
19 30 milligrams per kilogram, and this was based on
20 the pharmacodynamic effect. We didn't see any
21 difference. However, we do plan to continue to
22 look. We're looking at -- we have a study right

1 now in younger patient populations, and we have a
2 study in older populations. And we have plans to
3 go down to the newborn level, and we will be
4 looking at a number of different ways of dosing,
5 even at younger ages.
6 DR. ALEXANDER: Thank you. Dr. Onyike?
7 DR. ONYIKE: So I'm not exactly sure who I'm
8 directing this to, so please, Dr. Kaye or someone
9 else with the technical qualifications should take
10 the question. What I really want to understand is
11 about the mean relative fluorescence intensity.
12 I'm having difficulty understanding how it's a
13 quantitative measure because you're
14 essentially -- it seems to me you have pathologists
15 looking at slides and trying to make decisions
16 about the intensity of a dye relative to what scale
17 is very unclear.
18 But I can imagine that with the naked eye,
19 it's very hard to achieve very graded
20 quantification of staining unless you have some
21 sort of spectrum that you make a reference to,
22 which I don't think you have.

1 So explain how exactly we should take the
2 mean relative fluorescence intensity as seriously
3 as say, the Western blot, in terms of
4 quantification?
5 MS. RUFF: So to address your question about
6 quantification using intensity, I'd like Dr. Frank
7 to come to the podium.
8 DR. FRANK: Thank you. My name is Diane
9 Frank. I'm the senior director of translational
10 research at Sarepta. The intensity measures were
11 made using a computer algorithm, because as you
12 correctly stated, the human eye is not very good at
13 measuring intensity levels with the resolution that
14 the computer program's able to do. Because a
15 computer program has a definition to look at the
16 pixel intensities in the region of the membrane, it
17 can calculate the average intensity pixel by pixel
18 across the image.
19 DR. ONYIKE: If I may follow on, how do you
20 translate then these intensities into actual tissue
21 concentrations at the sarcolemma?
22 DR. FRANK: So one of the challenges in the

1 field is there is no absolute standard for
2 dystrophin, therefore, we have no ability to do an
3 absolute dystrophin concentration, such as a
4 microgram per square centimeter.
5 As a result, we make our comparisons to one
6 consistent normal control, and that's why you're
7 seeing percent normal. And then the change of our
8 therapeutic effect is a relative change due to the
9 lack of an absolute standard, so that we're looking
10 at the change from baseline.
11 DR. ALEXANDER: Thank you. Dr. Green?
12 DR. GREEN: Yes, I wanted to know whether
13 there was any specific language that was included
14 or excluded before the 6-minute walking test in
15 both subjects and the controls.
16 MS. RUFF: If I can just clarify. Are you
17 talking about the script for the 6-minute walk
18 test?
19 DR. GREEN: Well, I'm talking about -- no,
20 I'm actually talking more about in advance in
21 preparation for the 6-minute walking test, and not
22 only in those who had it administered as part of

1 the trial but in the control group.
2 MS. RUFF: So I'd like Dr. Mendell to talk
3 about the eteplirsen boys, and then Dr. Mercuri to
4 talk about the external control boys.
5 DR. MENDELL: Well, the 6-minute walk test
6 is done in a standard fashion. The boys are
7 explained the test prior to it being done. And
8 then during the trial, they, one, are told that
9 they must walk and not run, and they should try as
10 hard as they can. And there is encouragement for
11 them to continue the walk as long as they can.
12 If they fall, there is someone behind them
13 to, as you saw in the video, help them get up and
14 then continue to walk. For those boys who can't
15 continue because they have been injured or in pain
16 or whatever, then they will stop, and that will be
17 the end of the walk test.
18 But it's done in a standardized fashion.
19 The same therapist does the same test on every
20 single patient, and it's the same thing for our
21 clinic when the boys come, even outside of the
22 study.

1 DR. ALEXANDER: Can you speak into the
2 microphone please, Dr. Green?
3 DR. GREEN: And there are no family members
4 present during this?
5 DR. MENDELL: There are absolutely no family
6 members present when the boys are tested.
7 DR. MERCURI: The same applies for the
8 external controls. There is a manual. There are
9 strict instructions on how to perform it. It's the
10 same way we perform it in clinical routine and in
11 the clinical trials. And the instructions are very
12 strict also on the time of the encouragement and so
13 on.
14 So these children know the test very well
15 because it's part of our clinical routine. But
16 again, I want to stress that the training is very
17 specific on giving strict instructions according to
18 what is specified in the manual.
19 DR. GREEN: Thank you.
20 DR. ALEXANDER: Thank you. Dr. Nuckolls?
21 DR. NUCKOLLS: Yes, I have a question for
22 Dr. Mendell regarding --

1 DR. ALEXANDER: Could you please just state
2 your name on the record again?
3 DR. NUCKOLLS: I'm Glen Nuckolls. So a
4 question for Dr. Mendell regarding genotypes that
5 modify disease progression, such as osteopontin and
6 LTBP4. So you were an author on a publication in
7 2013 that demonstrated that the major protective
8 haplotype of LBTP4 is associated with prolonged
9 ambulation, up to 2 years, a level comparable to
10 the effects of corticosteroid treatment.
11 So what is known about the modified
12 genotypes of the treated and control groups and how
13 might that information aid in interpreting the
14 data?
15 MS. RUFF: One thing I'd like to point out
16 is the prevalence of these modifiers are very, very
17 low. But anyway, I will ask Dr. Mendell.
18 DR. MENDELL: Well, Glen, thanks for the
19 question. I think what you have to appreciate is
20 that back in 2010 when we designed this study,
21 there were no modifiers, and so it was not part of
22 the original protocol. And then, as the study

1 evolved and we saw the results, and then compared
2 it to the Italian group and the Leuven group, we
3 had comparable number of patients, comparable age,
4 and as Ed Kaye showed, they were matched
5 demographically in every way.
6 We appreciate that the modifiers would be
7 equally distributed between the groups. There's 12
8 in our group, 13 in the comparable control group.
9 And we felt that there would be the same
10 statistical possibility for the modifying mutation
11 to appear in both groups.
12 So it has not been done, but it could easily
13 be done at any point in time. It's unlikely to
14 have an effect given that the groups are the same
15 size. And in the Italian group, there is no
16 difference in terms of the 6-minute walk and so
17 forth, as you saw.
18 DR. ALEXANDER: So this is Caleb Alexander.
19 Just to clarify, you don't have information, it's
20 never been studied, for either the control or
21 treated patients, the presence of this genetic
22 phenotype?

1 DR. MENDELL: At this point, yes.
2 DR. ALEXANDER: Thank you. Dr. Ovbiagele?
3 DR. OVBIAGELE: Bruce Ovbiagele. My
4 questions pertain to the nature and the timing of
5 dystrophin, and so perhaps this question might be
6 for Dr. Kaye.
7 First, I recognize of course that it's the
8 increase from baseline that's the most meaningful
9 determination of treatment effect. But from the
10 literature, do we know what the magnitude of
11 increase from baseline that's most meaningful?
12 That's the first thing.
13 Secondly, have exon 51 patients actually
14 been studied with regard to that, and what exactly
15 is the clinical relevance?
16 The last question pertaining to that is
17 about dose and duration. Are there any other
18 supportive data at 24 weeks showing that there's an
19 increase in dystrophin at that time point?
20 MS. RUFF: So I'd just like to clarify your
21 question. So I believe you had three questions.
22 One was about increase from baseline, are there any

1 details in the literature.
2 DR. OVBIAGELE: Right. So on one particular
3 slide, it was pointed out that the increase from
4 baseline is the most meaningful determination of
5 treatment effect, and certain references were
6 cited. So I was trying to figure out what the
7 magnitude of that increase actually is and whether
8 exon 51 patients were actually studied, and what
9 was the actual clinical impact.
10 MS. RUFF: Okay. So I'll ask Dr. Kaye to
11 come first to discuss the magnitude of effect from
12 baseline, and then Dr. Muntoni to discuss the
13 clinical relevance.
14 DR. KAYE: One of the challenges of course
15 that we had with this study is there is no
16 information before this therapy was initiated. The
17 reason being is that no other drug has produced
18 dystrophin as a comparator, so we don't have a good
19 comparator to know how much is enough. The only
20 way we can compare is to know what's available in
21 the exon 51 boys and other boys who have certain
22 amounts of dystrophin.

1 What we do appreciate from the field is that
2 if you have a small amount of dystrophin, what's
3 been recorded in the exon 44 population, that does
4 seem to make a difference. You can prolong
5 ambulation by at least 2 years. So we have to make
6 that comparison by stretching to the literature,
7 but there is no baseline that has been established
8 because no one's really been able to make
9 dystrophin before to compare.
10 DR. MUNTONI: My name is Francesco Muntoni.
11 I'm a pediatric neurologist. I work at UCL in
12 London. I was a principle investigator the first
13 two clinical trials where this drug was given for
14 the first time to boys with Duchenne. I have
15 received compensation from Sarepta for being here
16 at this meeting, and I have no financial interest
17 in the outcome of the meeting today.
18 I will address two points from your
19 question. The first is, what is the significance
20 of this increase in this treated boy, and the
21 second is, has other patients with exon 51 been
22 studied.

1 So regarding the first point, as a person
2 who looks at the biopsy of these children as well,
3 one thing that is unusual in the biopsy of these
4 children that convinced me that there is a
5 functional significance of this level of dystrophin
6 is that not only there is dystrophin at the
7 sarcolemma but there is restoration of protein of
8 the dystrophin associated complex.
9 So dystrophin is a member of a protein
10 complex, and its deficiency leads to a
11 destabilization of a number of protein associated
12 with the sarcolemma. And in the fibers that have
13 dystrophin, you can see and also quantify using the
14 immunocytochemistry if the protein of the complex
15 have been restored.
16 I will ask in a second a slide to come up
17 where you will see that there will be black when
18 there is no dystrophin, there will be white at the
19 sarcolemma where there is dystrophin. And you will
20 see that whenever there is dystrophin, the protein
21 of dystrophin, as a safety complex had been
22 restored.

1 If I can have this slide up, please. So if
2 you concentrate on the left side of the screen, you
3 will see that every single circle on the top with
4 white is dystrophin. The same fibers in the
5 intermediate and lower panel also have other
6 dystrophin associated protein that are not present
7 in the fibers that do not have dystrophin. So that
8 I think is a very powerful argument that that
9 dystrophin is doing something functional.
10 In terms of the second part of your
11 question, if I understood it correctly -- will you
12 please correct me if I didn't -- so we did look at
13 a patient who have exon 51. They are the
14 equivalent of what we want to do by skipping exon
15 51. They are Beckers who have the equivalent
16 deletions. And I co-authored the paper that was
17 also cited in the briefing document for FDA.
18 So when we look in these patients, what we
19 found were two things that are important. The
20 first is that the level of dystrophin in this group
21 of patients was very high in general. The lowest
22 patient was in the range of 40 percent.

1 However, one important point to make, the
2 great majority of these patients were either
3 symptomatic or had minimal symptoms, and therefore
4 what we concluded is that if you were able to put
5 40 percent dystrophin, this patient potential could
6 be asymptomatic. So that of course is an
7 extrapolation regarding the treatment now.
8 Does that answer your question?
9 DR. OVBIAGELE: No, that's very helpful.
10 And just a last question, please, about the timing
11 of the increase in dystrophin, which was at
12 24 weeks, which was somewhat contradictory to one
13 of your earlier studies. And I wondered if there
14 any literature supporting that increase at
15 24 weeks.
16 MS. RUFF: Dr. Kaye?
17 DR. KAYE: So again, one of the limitations
18 is that there hasn't been any other drug that has
19 been able to really measure dystrophin. We know
20 that dystrophin lasts a very long time and has
21 about a 2-month turnover, so we know in order for
22 the protein to turn over and to make new one, it's

1 going to take a fairly long period of time.
2 What Dr. Muntoni had shown in his
3 laboratory, within the first 12 weeks, you could
4 see some dystrophin. He had a very sensitive
5 assay, but it wasn't as, let's say, reproducible
6 and validated as the second assay that we
7 performed.
8 But what we saw at 24 weeks is a consistent
9 increase in all of the patients, and this is
10 probably consistent with the half-life. So this
11 was really the first time that this has been
12 appreciated, and, again, because eteplirsen was
13 really the first drug to show dystrophin.
14 DR. ALEXANDER: Does that answer your
15 question? Okay.
16 So we'll take a question from Dr.
17 Kesselheim, and then after that, we'll convene for
18 a break.
19 DR. KESSELHEIM: I just wanted to follow up
20 on the dose question just to clarify how it was
21 that you determined the 30 and 50 milligram dose on
22 the basis of the prior studies that didn't test

1 that, and then how you determined to choose the
2 30-milligram dose as the one that you are
3 approaching. And then my other question is whether
4 you had a physiologic basis for the 24-week
5 hypothesis, but I think you addressed that in the
6 previous discussion.
7 MS. RUFF: Okay, so Dr. Kaye.
8 DR. KAYE: So as you can imagine in rare
9 diseases, dose ranging can be challenging because
10 you don't have large numbers of patients. So we
11 had determined early to do a dose ranging based on
12 the percent dystrophin positive fibers. And what
13 I'd like to show you is at our week 48 biopsy, we
14 had a comparison of the percent dystrophin positive
15 fibers and also the dystrophin intensity.
16 Slide up, please. In looking at this slide,
17 in the purple, we see the 30 milligrams and the
18 50 milligrams. And we see that they were very
19 similar for percent dystrophin positive fibers and
20 for intensity.
21 But obviously this is not a perfect dose
22 finding, and what we did do is an additional study

1 to look at 30 and 50 in addition to clinical.
2 Slide up, please. And when we compare to the
3 clinical 6-minute walk test distance, if we look at
4 the 30 and 50, they're very similar.
5 So based on these data, we decided that we
6 didn't know if there was any potential long-term
7 toxicity. We know this would be a lifelong
8 therapy. We chose the lower dose because we
9 couldn't see a difference. But I think as we go
10 forward, we will look at other dose regimens, and
11 potentially at higher doses, and just to make sure
12 that we understand how to properly use this drug.
13 DR. ALEXANDER: Thank you very much. We'll
14 now take a 15-minute break, so we'll return here at
15 10:55, promptly. Panel members, please remember
16 that there should be no discussion of the meeting
17 topic during the break amongst yourselves or with
18 any member of the audience. Once again, we'll
19 resume at 10:55 a.m.
20 (Whereupon, at 10:40 a.m., a recess was
21 taken.)
22 DR. ALEXANDER: We're going to get started.

1 If everyone can please take their seats, we'll
2 begin with the meeting.
3 Thank you. We'll now begin with the FDA
4 presentations, and first, we'll hear from Janet
5 Woodcock, director at the Center for Drug
6 Evaluation Research.
7 **FDA Remarks - Janet Woodcock**
8 DR. WOODCOCK: Thank you, Mr. Chairman, and
9 good morning. The purpose of today's meeting is
10 for FDA to get expert advice from the committee on
11 a marketing application for the drug eteplirsen.
12 And what I'd like to do is provide a framework
13 within which to consider these data based on my
14 30 years of experience at FDA and really extensive
15 experience in implementation of the legal standards
16 for drug approval.
17 The clinical development program for this
18 product has features that render the data
19 particularly difficult to interpret. It consists
20 primarily of long-term observation of a group of 12
21 treated individuals.
22 When a large treatment effect is observed,

1 for example significant improvement in a disease
2 characterized by overall progression, an
3 uncontrolled study can provide compelling data.
4 Where overall effects are smaller, and especially
5 if there's large inter-individual heterogeneity in
6 the disease course, interpretation of data like
7 this can be challenging.
8 The sponsor and FDA have attempted
9 interpretation by comparing the results in treated
10 children to the disease trajectory that is recorded
11 in a number of external cohorts. It's possible to
12 reach different conclusions about these comparisons
13 as is being discussed today.
14 Eteplirsen is intended to improve outcomes
15 in a targeted subset of DMD patients by enabling
16 muscle cells to produce a truncated version of the
17 protein dystrophin, which is missing or present at
18 very low levels in patients with DMD.
19 There is agreement that eteplirsen does
20 achieve its primary intended pharmacodynamic
21 effect, that is production of a truncated messenger
22 RNA, and this is based on PCR results from muscle

1 biopsies.
2 It was originally hoped that this effect
3 would result in a substantial increase in
4 expression of the truncated dystrophin molecule,
5 perhaps to the average level of individuals with
6 Becker muscular dystrophy. This has not turned out
7 to be the case. The increase in dystrophin so far
8 observed is a fold increase over baseline, well
9 below the average dystrophin content in individuals
10 with Becker muscular dystrophy.
11 Now, it hasn't been established for any
12 given person with Duchenne muscular dystrophy
13 whether a small fold increase in dystrophin will
14 provide clinical benefit, or whether there's a
15 threshold, for example an absolute percentage of
16 normal, that is required to deliver a benefit.
17 This is unknown, and of course the sponsor has just
18 argued based on observing other mutations that
19 perhaps small levels may be associated with
20 benefit.
21 It's unlikely an absolute threshold can be
22 established given the fact that within muscular

1 dystrophy, the phenotype, in other words the
2 disease expression, appears to be influenced by
3 factors beyond dystrophin expression, so there are
4 other factors at work.
5 Interpretation of dystrophin expression has
6 been complicated by many technical difficulties.
7 The FDA has put a huge effort into trying to render
8 the results interpretable, along with the sponsor.
9 To me, it is remarkable that the field of exon
10 skipping has advanced far into clinical development
11 generally without well-validated methods of
12 determining pharmacologic success, especially when
13 assessing this biomarker requires muscle biopsies
14 in children with compromised musculature, usually
15 under general anesthesia.
16 There are a lot of questions that still
17 remain, not just about quantitating the Western
18 blot, but also about specimen handling and intra-
19 and inter-muscle variability and results,
20 especially in later stages of disease. There are
21 also questions, and they've been raised today,
22 about the utility of the information supplied by

1 immunofluorescence techniques in comparison to
2 Western blot, and these questions are going to be
3 quite important today.
4 The translational science supporting these
5 development programs is inadequate, and this state
6 of affairs is not atypical in rare and not so rare
7 diseases, and it significantly hinders the tasks of
8 drug developers, as well as the FDA, in assessing
9 the results of these programs.
10 After the presentations by FDA, the sponsor,
11 and the public, the committee will be asked a
12 series of questions about the robustness of the
13 data support marketing approval, either regular
14 approval or approval under the accelerated pathway.
15 The determination that a drug's approvable
16 from a clinical standpoint is a two-step process.
17 First, a finding of substantial evidence of
18 effectiveness, usually based on clinical outcomes,
19 must be made, as Dr. Dunn said earlier. In the
20 case of accelerated approval, this finding can be
21 made based on substantial evidence using a
22 so-called unvalidated surrogated endpoint, believed

1 reasonably likely to predict clinical benefit.
2 Then, the second step after that is
3 determine whether the likely benefits of a drug
4 outweigh the foreseeable harms. And a final
5 approval decision from a clinical basis is whether
6 the benefits outweigh the foreseeable risks.
7 The issue of substantial evidence for
8 regular approval, in this case we're talking about
9 today, turns on how compelling you find the
10 comparisons to the external cohort data. I believe
11 the committee has experience with this question,
12 and so I'm not going to into it anymore.
13 Accelerated approval is a more nuanced
14 issue. In the FDA Safety and Innovation Act of
15 2012, Congress instantiated and statute our
16 accelerated approval regulations, and in doing so
17 urged FDA to apply accelerated approval more
18 broadly, particularly in rare diseases, while
19 maintaining our standards. FDA has never
20 articulated an evidentiary standard for determining
21 if a surrogate endpoint is reasonably likely to
22 predict clinical benefit.

1 In applications of accelerated approval
2 outside of cancer and HIV, FDA has used various
3 types of data, including natural history data,
4 pharmacologic, pathophysiologic, and clinical data
5 to assist with this determination in a wide variety
6 of settings, most of them rare disease settings.
7 The agency has exercised considerable flexibility
8 in applying these criteria of reasonably likely.
9 In the case before us today, the linkage
10 between the observed levels of dystrophin
11 expression and potential clinical benefit will be
12 explored. If the committee were to recommend that
13 the clinical data represent substantial evidence,
14 then the question of accelerated approval does not
15 need to be taken up by you.
16 If the committee does not make this finding,
17 then the clinical data generated in this
18 development program that you've heard about this
19 morning may be used as part of the assessment of
20 whether the surrogate of dystrophin expression at a
21 particular level is reasonably likely to predict
22 clinical benefit. And I'm happy to answer

1 questions later about that statement if you wish.
2 Finally, I would note that much of the
3 effort in evaluating a drug development program
4 goes into avoiding a specific mistake, that is
5 erroneously approving a drug that is not effective.
6 There often is little consideration of
7 another error, which is failing to approve a drug
8 that actually works. In devastating diseases, the
9 consequences of this mistake can be extreme, but
10 most of these consequences are borne by patients
11 who traditionally who have little say in how the
12 standards are implemented.
13 The accelerated approval program includes a
14 requirement for confirmatory studies for efficacy,
15 so as you've heard from the sponsor, you have to do
16 further studies to explore and confirm
17 effectiveness. An inherent presumption in this
18 program of accelerated approval, which is written
19 in the preamble to our regulation about it, is that
20 more uncertainty is going to be tolerated initially
21 and that in fact sometimes we will collectively get
22 it wrong, otherwise accelerated approval would

1 really have no different standards than regular
2 approval.
3 I hope these remarks have been helpful, and
4 I look forward to hearing the deliberations. Thank
5 you.
6 DR. ALEXANDER: Thank you. Next, we'll hear
7 from Dr. Robert Temple.
8 **FDA Presentation - Robert Temple**
9 DR. TEMPLE: Good morning. I'm going to
10 talk about historically controlled trials,
11 generally as a basis for what you would call full
12 approval. The point Dr. Woodcock made that there
13 are other ways to consider this is important.
14 So this will be a brief discussion of the
15 history of our use of historically controlled
16 studies and the concerns associated with the
17 design, which will I'm sure be quite familiar to
18 the committee. I want to emphasize, I am not in
19 any way addressing the eteplirsen data in study
20 201/202; that's going to come in subsequent
21 presentations.
22 Section 505(d) of the Food, Drug, and

1 Cosmetic Act defines the standards for drug
2 approval calling for substantial evidence of
3 effectiveness. I don't necessarily have to read
4 all this stuff, but it means evidence consisting of
5 adequate, well-controlled studies that allow you to
6 reach a good conclusion.
7 Adequate and well-controlled studies were
8 actually first defined in regulations in 1970, a
9 long time ago, and they are now in 21 CFR 314.126
10 in the current regulations. And from the
11 beginning, they've always included as one kind of
12 adequate and well-controlled study, the historical
13 control, which is interesting because a lot of
14 people would have considered those not quite
15 controlled studies. But it's always been part of
16 it, absolutely part of it.
17 This is what the regulation says. Sorry to
18 have to read so much. "The results of treatment
19 with the test drug are compared with experience
20 historically derived from the adequately documented
21 natural history of the disease or condition, or
22 from the results of active treatment in comparable

1 patients or populations.
2 "Because historical control populations
3 usually cannot be as well assessed with respect to
4 pertinent variables as can concurrently controlled
5 populations, historical control designs are usually
6 reserved for special circumstances, and the
7 examples include studies of disease with high and
8 predictable mortality, like certain malignancies,
9 and studies in which the effect of the drug is
10 self-evident, general anesthetics, drug
11 metabolism."
12 Note, although this isn't specifically
13 discussed, that a baseline control trial where a
14 single arm treatment is compared with what would
15 have been expected in the absence of an
16 intervention is a kind of historical control,
17 although it's not generally mentioned.
18 ICH E-10 went into a number of different
19 kinds of controls, non-inferiority studies and
20 others, but it also spent some time on the
21 historical control and renamed it as a kind of
22 quote, "external control."

1 It notes several different kinds. One is a
2 population treated earlier. That's really a
3 historical control. A population treated
4 contemporaneously at another institution. That's
5 not exactly historical but it is external. It
6 could be a group outside the study within the same
7 institution. And it identified specifically the
8 baseline control where the patient's course is
9 compared with the expected course, always a
10 difficult thing. And it again notes the design is
11 most clearly usable when the effect is dramatic and
12 rapid.
13 ICH E-10 goes at some length into what the
14 difficulties are with these trials, and the major
15 one, of course, is the inability to control bias,
16 which is a major and well-recognized limitation of
17 externally controlled trials and in many cases
18 makes the design unsuitable.
19 It's worth noting the really two distinct
20 aspects of bias. One is bias before the trial,
21 that is, in who you put into the study, and then
22 the other is bias during and after the trial, sort

1 of bias in the observations.

2 Bias before the trial refers to patient

3 selection. Who have you put into the trial? But

4 even that is really two issues. One, since you

5 don't really know, you're not randomizing, the

6 groups can be non-comparable in ways that you don't

7 really understand because you haven't randomized.

8 Randomization doesn't always lead to comparability

9 either, but in something like this it's more of a

10 problem.

11 The other part of this is selection bias;

12 that is, the control patients could be chosen in a

13 way that means they're sicker. That's

14 non-comparability, but it's got a bias in it. So

15 those are two slightly different aspects of it.

16 As I said, non-comparability of a random

17 nature can go in either direction. It might not

18 favor the treatment. But the guidance, the E-10

19 particularly, notes that it is well-documented that

20 untreated historically controlled groups tend to

21 have worse outcomes than an apparently similar

22 chosen control group in a randomized study,

1 possibly reflecting a selection bias.
2 There are some examples of this of a classic
3 nature. One of my favorite papers was one by
4 Sacks, Chalmers, Smith and coworkers in 1982 that
5 compared randomized trials and historically
6 controlled trials for the same disease, finding
7 results regularly more favorable for the
8 historically controlled trials.
9 The following figure was created by
10 Dr. Unger from a table in this paper, and it's
11 clear that the results of randomized trials are
12 regularly less positive than historically
13 controlled trials. In the examples given in the
14 paper, there were 10 out of 50 that were favorable
15 for the randomized trials and 44 out of 56
16 favorable for the historical controlled trials, and
17 that's what it looks like.
18 The historically controlled trials are on
19 the left, the randomized are on the right.
20 Effective means red. And you can see that in
21 randomized trials in the cirrhosis, surgical
22 treatment to prevent variceal bleeding, in coronary

1 artery surgery, and so on, the historically
2 controlled trials almost always do better.
3 One particular example was a pooled analysis
4 of shunt surgery for preventing bleeding in
5 cirrhotics, and you can see that the bottom line
6 there, which is the historical control, they do
7 much worse than the randomized treatments. My
8 explanation of this has always been that surgeons
9 don't like to lose, so they put healthier people
10 into their control group when they're in control of
11 the assignment.
12 So it seems very likely that in general in
13 Chalmers' studies, the historical control untreated
14 patients were sicker than the surgical candidates
15 in the randomized trials. Selection bias in this
16 case, with patients being different at baseline, is
17 the only real source of potential bias here.
18 Mortality is objective. We don't think that could
19 have been done in a biased way. But the baseline
20 differences could have been very important.
21 So ICH E-10 specifically notes that
22 selection of the control retrospectively with the

1 results known and in hand poses a particular
2 problem.
3 There could also be biases during and after
4 the trial, and you'll hear discussions of some of
5 these things. But the lack of blinding and the
6 investigator's knowledge of treatment in patients
7 getting the test treatment can also allow bias to
8 affect endpoints if they have subjectivity in them.
9 And many endpoints, even ones you might think are
10 highly objective, have a subjective element,
11 including whether a person's had a heart attack or
12 not, cause of hospitalization, and most of the
13 other endpoints we typically use. That is why we
14 blind the people who decide those things.
15 You'll hear later a discussion of the
16 possible subjectivity of ability to ambulate.
17 There will be a debate about that, of course. But
18 importantly, expectation bias and motivation can
19 very markedly affect symptoms and performance, and
20 there are some examples I'll show you where that
21 seems to have been the case.
22 There can also be other biases, I won't

1 dwell on this, but the choice of endpoints. You
2 know, in a controlled trial, you choose the
3 endpoints beforehand. When you're looking at data
4 after the fact, you can look around.
5 So in ICH E-10, the overall tone is
6 relatively skeptical about the use of external
7 controls for most situations, as is also our
8 adequate and well-controlled studies regulation,
9 but both accept them as credible in particular
10 situations.
11 What ICH E-10 urges is selection of a
12 control group for which there's detailed
13 information: demographics baseline state,
14 concomitant medications, and steady course, and
15 you've already heard from Dr. Kaye arguments that
16 that is in fact what they did; try to assure
17 similar treatment other than the test drug and
18 similar observations in the treatment and control
19 groups. It's not a bad idea to have multiple
20 external control groups if you can do it; and it
21 doesn't come up here, consideration of blinded
22 endpoint reassessment in the treatment and external

1 control groups, which can be done sometimes.
2 ICH E-10 also suggests that the main
3 credible use of external controls is when there's
4 ethical difficulty in doing the randomized trial.
5 They strongly urge early randomization, which
6 certainly we've urged in many other cases.
7 The concurrently controlled trial can detect
8 extreme effects very rapidly and can detect modest
9 but still valuable effects that would not be
10 credibly demonstrated by an externally controlled
11 trial. And ICH E-10 again notes that external
12 control trials are most likely be persuasive when
13 the effect is large.
14 Just a couple of more examples that have
15 always interested me. This first one was of
16 interest to me because the person who wrote the
17 letter I refer to there was my first attending at
18 Columbia, a guy named David Gocke, an infectious
19 disease guy.
20 So he wrote a letter to the New England
21 Journal in 1971 about fulminant hepatitis B treated
22 with serum containing antibody to what I used to

1 call the Australian antigen. They had 9
2 consecutive cases of acute fulminant hepatitis B.
3 All were fatal even though they did exchange
4 transfusions, gave steroids, and provided other
5 support. Then they treated eight coma patients
6 with the same treatment plus an anti-Australian
7 antigen, and 5 out of 8 survived.
8 And his letter to the New England Journal
9 says, you know, we thought maybe we were done, but
10 then we were worried that the treatment -- that
11 there's better care, earlier treatment, so we urged
12 a randomized trial, and they did one, in which he
13 participated.
14 This was published in 1977 in the Annals of
15 Internal Medicine. There were 53 patients at
16 30 centers. Survival was as follows. In the
17 placebo group it was 9 of 28, or 32 percent, in the
18 people who got the antigen it was 28 percent.
19 There was no effect at all; pretty sobering and
20 hard to understand given the early results.
21 More recent example, you've all probably
22 read about this, a widely publicized renal artery

1 denervation device was studied in three trials.
2 The first one was an open-label single-arm study
3 called SYMPLICITY HYPERTENSION-1. It found an
4 average 3-year fall in blood pressure of 33/19.
5 Pretty impressive. This was in people who aren't
6 responsive to other stuff.
7 Then they did a randomized trial, device
8 versus no device, but no sham control, and they
9 found an almost identical effect. Finally, they
10 did a randomized trial with a sham control,
11 SYMPLICITY 3, and they found at 6 months a change
12 of minus 14 in the denervation population versus
13 12 millimeters in the sham operation. Nothing. So
14 again, sobering on what seems like a very objective
15 endpoint.
16 Then Dr. Unger has provided me with help on
17 transmyocardial laser revascularization therapy.
18 That's where you make holes in the heart to allow
19 blood to flow, and this is what you do. You use a
20 laser to make holes in the heart and allow blood to
21 go in.
22 Initially, at least, it required open heart

1 surgery to use the laser to create channels through
2 the heart muscle, and no one thought you could do a
3 placebo-controlled -- sham-controlled trial -- if
4 you had to do open-heart surgery, so that was
5 pretty reasonable.
6 The results were very striking. This was
7 effects on exercise tolerance for angina, a typical
8 test for angina. So I'm showing two studies here.
9 One showed a gradual increase over time for
10 12 months, almost a doubling of the exercise
11 ability, and the second trial shows almost the same
12 thing. The effects were sustained over a year. It
13 really seemed beyond what anybody could imagine a
14 placebo response was.
15 Then it became possible to do these things
16 without open-heart surgery through catheters. So
17 they did a double-blind, placebo-controlled trial
18 in almost 300 patients comparing 2 doses as well as
19 no treatment, comparing to a sham procedure. And
20 as you can see, there was just no effect at all.
21 All of this is obviously very sobering.
22 So having said that, we do rely on

1 historically controlled trials, just as the
2 regulations contemplate. And the question always
3 is, when are they credible enough and when are they
4 not. There are some obvious cases where it's
5 reasonable.
6 When I was in training, leukemias were
7 always fatal within 3 months, and then there began
8 to be treatments where there were cures. Well,
9 that never happened. You didn't need a control
10 group to know that that couldn't happen.
11 The first three treatments for metastatic
12 testicular cancer, at least some of which I signed
13 off on, were cisplatin, ifosfamide, and etoposide.
14 They were all based on success rates in people with
15 metastatic disease, who would not have been alive
16 at one year, much less alive and tumor free. And
17 in the case of cisplatin, it was 90 percent
18 tumor-free survival at one year. You didn't need a
19 control group to know that that worked. So those
20 were very, very easy.
21 Less easy, but we did it anyway, when I was
22 directing the cardio-renal division a long time

1 ago, we used to approve drugs for stone disease
2 based on comparing the stone rate in the 6 months
3 before they got the drug with the stone rate in the
4 next 6 months or 3 months -- I don't remember
5 anymore -- and we approved the drugs because the
6 differences were large and persuasive. I don't
7 know if we'd still use that trial design today, but
8 we did then and we were perfectly happy with it.
9 Then, in many orphan diseases where the
10 course is clear and very well-known, we do use
11 these designs. Alglucosidase alpha for Pompe
12 disease in 2006, the endpoint was 1 year
13 ventilator-free survival in 18 treated patients
14 versus 62 historical controls. I didn't put the
15 response rates here, but 15 out of 18 in the
16 treated group survived and 1 out of the 62 in the
17 historical controls survived that time. Pretty
18 persuasive. It would be hard to argue.
19 There are others. Lomitapide was approved
20 for LDL cholesterol lowering in patients with
21 familial hypercholesterolemia. Huge change in LDL,
22 obviously not something that could happen

1 spontaneously. And then a treatment of Cushing's
2 disease markedly lowered urinary free cortisol.
3 Again, that doesn't happen in people with that
4 disease. And then deferiprone was approved in 2011
5 for treatment of iron overload, and again marked
6 changes showing reduced ferritin in something that
7 almost surely would not have changed. So those can
8 be persuasive.
9 There have been anti-infective approvals
10 where we didn't think you needed to compare the
11 drug to existing therapy. It wasn't a question of
12 relative effectiveness, but where getting rid of
13 the organism was self-evident evidence that the
14 drug worked. So those are all cases where we found
15 historical controls persuasive.
16 The ones I've cited are typically cases
17 where there were very well-defined diseases with
18 very predictable outcomes, where you really didn't
19 think that the benefits could have been the results
20 of treatments other than the test drug, and where
21 the course was thought to be very variable.
22 There are obviously, and you're going to

1 hear one, cases in which there could be a debate
2 about how predictable the course of the disease is
3 in the absence of treatment, and thus whether
4 historical controlled approaches can be considered
5 and would be well supported as stressed in
6 ICH E-10, and that's what the discussion is about.
7 Thanks.
8 DR. ALEXANDER: Great. Thank you very much.
9 Next, Dr. Ronald Farkas and Dr. Ashutosh Rao
10 for the FDA efficacy review.
11 **FDA Presentation - Ashutosh Rao**
12 DR. RAO: Good morning, everyone. Thank you
13 for being here. I'm Dr. Ashutosh Rao. I am a
14 reviewer and researcher in the Office of
15 Biotechnology Products at the FDA. I provided the
16 clinical review team with a consult review of the
17 dystrophin bioassays and the supporting assay
18 validation information, some of which that you've
19 seen before and more will be presented today.
20 The FDA efficacy review will be presented by
21 both myself and Dr. Ronald Farkas, a clinical team
22 leader in the Division of Neurology Products in

1 CDER, FDA.
2 I'm going to start by discussing the assay
3 methods used to gather data about biomarkers in the
4 eteplirsen drug development program. Dr. Farkas
5 will then follow up to discuss the biomarker data
6 in detail and the clinical findings that go with
7 them.
8 Eteplirsen is proposed to increase the
9 production of exon skipped and truncated
10 dystrophin. The goal of my slides is to describe
11 to the committee and the audience how this
12 important endpoint for a proposed exon skipping
13 therapeutic was tested by the applicant, Sarepta.
14 I will provide an overview of our
15 understanding of the applicant's methodologies, our
16 understanding of the caveats of each of them, our
17 current thinking on the extent to which they can or
18 cannot analytically provide you with reliable data
19 indicating whether exon skipped dystrophin was
20 produced by eteplirsen, and if so, how much.
21 We would like you to consider these
22 technical caveats as you consider and discuss the

1 merits of the clinical findings presented by the
2 applicant and by FDA.
3 As stated previously by Dr. Dunn and by
4 Dr. Woodcock, FDA understands that lack of
5 dystrophin causes DMD and is very interested in
6 dystrophin as a biomarker and potential surrogate
7 for accelerated approval for drugs for DMD. Such
8 an approval would be based on a conclusion that the
9 dystrophin produced by a drug is reasonably likely
10 to predict clinical benefit. Reasonably likely
11 seemingly must depend on the amount, location, and
12 function of the dystrophin produced by the drug.
13 It is important to stress the need for
14 reliable assays and consistent findings to support
15 potential accelerated approval based on dystrophin
16 expression. Hence, the first part of the FDA
17 presentation will focus on FDA's views on the
18 methods and the results of dystrophin measurement
19 for eteplirsen.
20 Our current knowledge of dystrophin
21 bioassays based on literature and input from
22 several experts around the world is that a

1 scientific understanding of dystrophin requires
2 that the method or methods, a combination of
3 methods perhaps, be capable of answering basic
4 questions about the relative levels of dystrophin
5 mRNA and protein, its location, whether the newly
6 expressed dystrophin is increased beyond the
7 baseline levels of trace or revertant dystrophin,
8 and if it is functional in muscle fibers.
9 This slide lists the three common methods
10 used to show production of skipped messenger RNA
11 and dystrophin protein, reverse transcriptase PCR
12 for mRNA, and protein measurements using either a
13 Western blot or immunofluorescence-based method.
14 Each is a variation of a standard
15 methodology that's used in most laboratories, but
16 adapted for this large and very complicated
17 427 kilo Dalton protein. As a reminder, revertant
18 dystrophin, which arises from rare spontaneous
19 restoration of dystrophin in Duchenne patient
20 samples, is also present in each of the samples
21 that's going to be shown today and was shown
22 previously by the applicant and cannot be

1 distinguished from non-revertant dystrophin using
2 the currently used methodologies being discussed
3 here.
4 For each method, I will briefly highlight
5 the type of data submitted by the applicant and
6 summarize our current thinking of whether the
7 approach is analytically capable of providing
8 meaningful results. A typical data set from the
9 applicant's qualitative RT-PCR consisted of a gel,
10 as shown here on the slide, showing the presence or
11 absence of the skipped band representing the
12 expression of an exon 51 skipped dystrophin mRNA,
13 which reflects the fundamental and proposed
14 mechanism of action for this drug, eteplirsen.
15 As you can see from the example data set
16 here and by the red arrows on the slide, the
17 applicant's method is capable of demonstrating
18 whether or not skipped mRNA was produced.
19 A positive RT-PCR supports eteplirsen's
20 putative mechanism of action, but keep in mind that
21 the method is not quantitative. It does not
22 measure the number of copies of mRNA or test the

1 stability of this very large and unstable mRNA. It
2 has the largest exon set of sequence in the genome
3 at 79, so it is a very unstable mRNA.
4 Moreover, the production of mRNA being one
5 step prior to protein synthesis provides no
6 information on the protein itself, no information
7 on whether even protein was made from that mRNA.
8 Or whether that protein was functional, in other
9 words, whether it was capable of functioning as
10 normal dystrophin would in muscle fibers.
11 In order to detect dystrophin protein, the
12 applicant used either immunofluorescence or Western
13 blotting methods. The next few slides address
14 immunofluorescence. There are two endpoints used
15 by the applicant to present immunofluorescence
16 data, first by measuring fluorescence signal
17 intensity of microscopy generated images using a
18 computer software. The second is by scoring fibers
19 that are either positive or negative for an
20 anti-dystrophin antibody based fluorescence signal.
21 The applicant's immunofluorescence method is
22 capable of showing the location of dystrophin

1 protein based on reactivity with an anti-dystrophin
2 antibody. However, it is not designed to be truly
3 quantitative and compared to Western blotting has
4 serious shortcomings when it comes to quantifying
5 the levels of protein. Specifically, the intensity
6 measured by microscopy does not use healthy samples
7 of serial dilution or a reference standard of say
8 recombinant dystrophin protein or a fragment of the
9 protein that one would need to reliably compare and
10 objectively quantify the immunofluorescence signal.
11 During our review, we noted that the
12 intensity measurements tend to overestimate the
13 dystrophin fluorescence, especially at low levels
14 that are present in untreated and in some treated
15 samples. For instance, immunofluorescence signal
16 may indicate 10 percent of signal compared to a
17 healthy tissue specimen, but it would be far less
18 when the same sample, the exact same sample would
19 be tested by Western blotting.
20 The second immunofluorescence method used by
21 the applicant reports a score of dystrophin
22 positive fibers or percent positive dystrophin

1 fibers. This is also a standard technique. It's a
2 standard technique adapted but primarily
3 well-suited to confirm the location of proteins in
4 tissue sections.
5 On the right-hand side on top here is a
6 processed image of muscle section stained to
7 identify dystrophin. In this case the colors on
8 this image were inverted and amplified by the
9 applicant to allow a pathologist to score the
10 fibers.
11 You can see that the staining for dystrophin
12 by the applicant localizes to the sarcolemma as
13 would be expected. Staining fibers such as the
14 ones in this image are used to then score them as
15 dystrophin positive or negative. However, the
16 scoring is based on staining intensity and is not
17 an all or nothing type of scoring, and hence the
18 reading is subjective. For instance, fibers can be
19 classified as positive if the staining is only
20 barely above the background, as is the case in some
21 of the fibers here.
22 The staining between patients, and even

1 within the same patient but different muscle groups
2 or a biopsy taken on different days, is not uniform
3 and contain a mix of staining intensities. Also,
4 it is simply not possible to differentiate fibers
5 with new drug-induced dystrophin from the
6 spontaneously occurring revertant fiber dystrophin
7 using this method.
8 In general, for any fluorescence analyses to
9 provide reliable findings, here are some critical
10 factors that need to be part of a predefined study
11 design. The investigators need to be blinded to
12 patient identity and treatment assignment. There
13 should be a systematic and random selection of
14 fields, even better if this is automated.
15 Control sections with positive,
16 intermediate, and negative samples can estimate the
17 range of the signal obtained by one's test sample.
18 So even though the method is not quantitative, if
19 you were to use appropriate controls, you could at
20 least determine a range of your signal.
21 Careful consideration needs to be given to
22 how the image is processed, displayed, and even the

1 consistency and ambient light can be an important
2 factor. Independent reassessment by more than one
3 pathologist and blinded sequence for reading can
4 also help control for inter- and intra-observer
5 variability.
6 We believe that the data generated from
7 studies 28 and the early biopsies from
8 study 201/202 were largely exploratory, not
9 validated, and not consistent with all these
10 principles highlighted here.
11 Appreciating the potential significance of
12 dystrophin measurement towards the development of
13 much needed therapies for DMD, we worked very
14 closely with this and other applicants to clarify
15 and improve the scientific credibility of their
16 dystrophin findings.
17 Following discussions with the applicant and
18 the investigators, we scheduled and visited the
19 laboratory testing site at Nationwide Children's
20 Hospital to assess methodology and raw data where a
21 number of issues were identified. Extensive
22 technical advice was provided to the investigators

1 during and following the visit.
2 As has been mentioned before, we also held a
3 NIH/FDA joint workshop bringing together experts in
4 the field to discuss the current state of
5 dystrophin methodologies. Also, with input from
6 external stakeholders, FDA released a draft
7 guidance for industry on developing therapies for
8 DMD that included some guidance on the potential
9 for dystrophin to validate the findings of other
10 endpoints.
11 Following several rounds of discussion with
12 the FDA, the applicant developed and implemented a
13 technically satisfactory set of methods for
14 immunofluorescence. Specifically, they implemented
15 a systematic and random field acquisition protocol
16 for image acquisition, improved blinding processes,
17 implemented quality assurance steps, and
18 independent reassessment by three pathologists
19 outside the primary testing lab was carried out.
20 The experimental analyses included positive,
21 negative, and intermediate control samples in the
22 form of healthy Duchenne and Becker tissue

1 sections.

2 This slide shows an example of data from the
3 applicant's fourth biopsy showing two images on top
4 that are stained for dystrophin and the two
5 corresponding inverted and amplified images on the
6 bottom that were used for the pathologist to
7 identify total fibers.

8 The images that are on top are stained red
9 where the antibody had reacted with an
10 anti-dystrophin antibody. Both images contain
11 fibers scored positive by the applicant. However,
12 as I stated earlier, it is not possible to
13 differentiate between dystrophin spontaneously
14 present in revertant fibers and drug-induced or
15 newly expressed and truncated dystrophin. For
16 instance, it may be tempting to believe that
17 particular fibers in both of these images represent
18 drug-induced dystrophin, but there is no way to
19 know whether they are revertant or not using this
20 particular method. Analytically,
21 immunofluorescence is unable to tell us whether
22 dystrophin is new or not.

1 Also, the method cannot provide data on the
2 absolute levels of new truncated protein that
3 correspond to a given fluorescence intensity. From
4 the applicant's data, we can however tell that the
5 dystrophin as present in these samples is localized
6 to the sarcolemma region of the cell or the fiber,
7 which is where you would expect it to be if it were
8 functional.
9 Overall, we believe that the applicant's
10 overall immunofluorescence methodologies, both of
11 them, are capable of confirming location and are
12 supportive but tend to overestimate the signal
13 compared to other methods and cannot differentiate
14 between drug induced and truncated dystrophin from
15 the other forms of spontaneously occurring
16 dystrophin.
17 The next few slides cover the Western
18 blotting. The applicant's Western blot measures
19 the relative amounts of this 425 kilo Dalton
20 protein that reacts with an anti-dystrophin
21 antibody. This is the most quantitative method
22 used by the applicant and the best to compare the

1 relative levels of signal in samples in Duchenne
2 either before and after treatment, and comparing it
3 to Becker dystrophy or healthy control samples.
4 Although this method is technically
5 challenging, the image shown on this slide from a
6 1989, as has been said before, is representative of
7 a significant body of literature that suggests that
8 Western blotting can be performed reliably using
9 human tissue.
10 During discussions with the applicant and
11 the collaborating investigators about study 28 and
12 early biopsy data from study 201/202, several
13 concerns were identified in the methods that
14 obscured interpretation of the dystrophin data.
15 The full length gel image shown on the
16 right-hand side is an example of Western blotting
17 data from the bicep muscle tissue of the early
18 three biopsies in 201/202. On the left is from
19 study 28. As you can appreciate, the gels were
20 overloaded and the bands consequently were
21 oversaturated.
22 Because this method critically depends on

1 the presence of clear, distinct bands used for
2 quantitation based on the density of those
3 individual bands, these blots cannot provide
4 reliable quantitation of dystrophin protein.
5 Overall, the methods of dystrophin protein
6 quantitation from the first three biopsies in
7 study 201/202 were not considered reliable, and the
8 results were not considered interpretable.
9 Here the left image again shows the results
10 obtained before technical advice provided by the
11 FDA. The right side is from a fourth biopsy sample
12 after discussions with the FDA and using deltoid
13 muscle. While this slide should really require no
14 explanation, you can see how the Western blot
15 images from the early biopsies were clearly not
16 discernable to allow meaningful quantitation.
17 The red arrow on the gel on the right-hand
18 side shows the proposed location of the 427 kilo
19 Dalton protein that was then used for quantitation.
20 We consider the quality of the fourth biopsy set of
21 data to be satisfactory to quantify relative
22 protein levels.

1 This slide is meant to illustrate why we
2 consider the fourth biopsy data to be reliable,
3 essentially because of the inclusion of a standard
4 curve of serially diluted healthy samples on each
5 gel that are shown on the legend on the top of that
6 gel.
7 The presence of these serially diluted
8 samples allows the generation of a standard curve.
9 The curve is shown on the right, and the samples
10 were quantitated in the validated range of 0.25 to
11 4 percent of healthy dystrophin. We also consider
12 the fourth biopsy method to be more reliable
13 because of the inclusion of either a Duchenne or a
14 Becker, and a healthy control in the same
15 experiment corresponding to negative, intermediate,
16 or positive controls to allow a credible side-by-
17 side comparison of relative differences.
18 The fourth biopsy was acceptable but
19 problems with controls make the change in
20 dystrophin challenging to interpret. Ideally, the
21 change in dystrophin would have been assessed by
22 comparing pre-treatment samples to post-treatment

1 samples from the same patient and the same muscle,
2 but this is not how the analysis was conducted.
3 Here are some specific issues that were
4 identified with the choice of controls prior to the
5 fourth biopsy experiments that you should consider.
6 These are important to consider because the
7 applicant is proposing changes in dystrophin levels
8 following eteplirsen treatment when the samples
9 were tested and compared to this set of control
10 samples and not to each patient's matched baseline.
11 As mentioned before, different muscle groups
12 from treated samples were used for the analysis,
13 including the fourth biopsy where deltoid samples
14 were used in contrast to biceps from the first
15 three biopsies.
16 As a reminder, there were no deltoid
17 baseline samples for the same patients for
18 comparison and matched baseline samples were used
19 for only 2 of the 11 patients, and those two were
20 from a different muscle group, biceps in those
21 cases.
22 The DMD negative control samples that were

1 used for comparison were also from different
2 muscles, essentially including biceps, quadriceps,
3 and deltoid. And the data from all of these
4 different muscle groups were combined for a
5 comparison to the fourth biopsy data that was from
6 deltoid muscle.
7 The controls were not sex matched because
8 one female sample was included in the set of
9 samples used to calculate the mean healthy value.
10 And even within the healthy control data set, there
11 is variability as was seen in the reported range of
12 51 to 95 percent.
13 In summary, at this time, we believe that
14 the applicant's fourth biopsy data methods for the
15 201/202 study were the most quantitative and were
16 reasonably adequate for determining the relative
17 dystrophin levels for the purpose of their drug
18 development program, with the caveat that there are
19 some issues with the control sample that make it
20 difficult to accurately calculate the change from
21 baseline that could be caused by eteplirsen
22 treatment.

1 We also believe that immunofluorescence can
2 provide supporting information. It cannot reliably
3 quantitate dystrophin protein levels. It is
4 capable of informing on the location of potentially
5 newly expressed protein.
6 Overall, a combination of the applicant's
7 methods, immunofluorescence and Western blotting,
8 was considered reasonably capable of demonstrating
9 an increase in dystrophin by eteplirsen.
10 I will now turn it over to Dr. Farkas to
11 present the clinical findings from the applicant's
12 studies and their relevance.
13 **FDA Presentation - Ronald Farkas**
14 DR. FARKAS: Good morning. I'm Ron Farkas,
15 a clinical team leader in the Division of Neurology
16 Products at FDA. And the first thing I'd like to
17 say is that I've had the opportunity to talk to
18 Duchenne patients and caregivers at meetings
19 before, and I'm really glad that I've been invited
20 to talk at a parent project muscular dystrophy
21 meeting. And one of the things that I raised at
22 that meeting is it's really important to take a

1 close look at what you're being told and the kind
2 of analyses that are being done.
3 That was about a year ago, and there really
4 wasn't really an opportunity to go into the data,
5 and I would have really liked to then. But now we
6 have an opportunity to go closely into the data and
7 the way the data is being analyzed.
8 I'd just like to perhaps take a slightly
9 unusual approach and go for some slides in the
10 middle of my presentation because I think that what
11 might be in people's mind is that there's a very
12 large clinical effect, that all the control boys
13 are no longer walking and almost all the treated
14 boys are still walking.
15 So there's going to be a lot of talking, and
16 I'm going to explain a lot of sources of difference
17 between patients in drug trials and natural history
18 trials. So as I go through all that detail, I just
19 wanted to, again, kind of show people right now
20 where I'm headed to and to get people to think
21 about what the observations are showing.
22 If I could just have slide 67 pulled up.

1 It's going to take me a while to get to through
2 slide, but I think that one of the key things I'm
3 going to try to explain is that the way to look at
4 this data is to take a look at age of loss of
5 ambulation and not time to loss of ambulation.
6 One of the things I'm going to be driving at
7 is that contrary to what is suggested by some of
8 the applicant's analyses, there does not appear to
9 be evidence of a difference in age or future age.
10 And that future age is important, future age of
11 loss of ambulation in the eteplirsen patients and
12 controls.
13 So this graph shows, going from left to
14 right, it shows 6-minute walk test on the Y-axis
15 and age on the X-axis. And it shows going from
16 left to right, basically an alteration between the
17 course of the blue control patients and the red
18 eteplirsen patients.
19 So kind of going over at 200 meters -- so
20 going over, there's a blue patient and then a red,
21 a red, a blue, a blue, a red, a red, a blue over at
22 200. And I think one of the -- so let me just step

1 over here for a second.
2 So what's going on is that we're comparing
3 two different kinds of Kaplan-Meier curves to each
4 other. I'll explain that in a second, too. But
5 the blue patients have all gone down to zero in
6 6-minute walk test, and so the red patients
7 haven't, but we have to be very careful about if
8 we're thinking of what their age is or what their
9 walking ability is. Anyway, I'll get back to that
10 in just a minute.
11 I think the other slide I'd like to show is
12 slide 75. I think the issue here, and I'm going to
13 come back to this later, is the age or the
14 percentage of the patients that maintain ambulation
15 to 16 years old. So what we need to do is try to
16 picture what percentage of the eteplirsen treated
17 patients are going to be walking at age 16. And
18 actually it's older than age 16, so there's been
19 discussion about what age exon 51 patients walk to.
20 The best numbers that we have are 25 percent
21 at age 16, but actually there's -- and I'll get to
22 these slides later when I go through in order -- is

1 that 15 percent of patients are walking until
2 age 18.
3 So I'm going to start going back now to all
4 the details of -- well, perhaps all the small
5 things and all the medium sized things that add up
6 to problems with interpretation. But I think just
7 to start out with perhaps trying to show the way
8 that we've seen the data, that there is not this
9 very large difference in the age of loss of
10 ambulation between the treated patients and the
11 natural history patients.
12 So I'll go back. Could I have slide 21?
13 Just to go back to the beginning. I'm not going to
14 spend a lot of time describing the studies that
15 were conducted by the applicant because they did
16 that, but I'd like to focus on the advice that FDA
17 gave to the applicant and on the study results.
18 Phase 1 and 2 studies are important in drug
19 development. Study 28 was designed to identify a
20 route of administration and dose of eteplirsen that
21 might be effective. For most new drugs, and
22 especially those for serious diseases, the dose

1 should be increased until limited by safety or
2 tolerability or until there's no further increase
3 of a biomarker such as dystrophin in this case.
4 The eteplirsen doses in study 28 ranged from 0.5 to
5 20 milligram per kilogram per week, with 4 or fewer
6 patients in each dose cohort.
7 The study 28 investigators reported
8 dystrophin levels from zero to 5 percent of normal
9 in untreated patients, and that's an amount that
10 fit expectations for the trace levels of dystrophin
11 that are present in untreated DMD patients. The
12 investigators also reported finding dystrophin
13 levels after 12 weeks of eteplirsen treatment of 10
14 to 20 percent of normal, and that's an important
15 number to keep in mind because the experts, when
16 they saw that 10 to 20 percent, they were
17 encouraged, and that fit the expectations of
18 experts about the amount of dystrophin that might
19 result in clinical benefit.
20 No safety issues were identified that would
21 limit higher dosing. The highest dose was
22 20 milligram per kilogram per week. This lack of

1 toxicity is of course good, but only good in some
2 ways because it also represents a shortcoming, a
3 missed opportunity to study higher doses.
4 The next study, 201/202, tested doses only
5 modestly higher than 20 milligram per kilogram per
6 week. That is not much higher than in study 28.
7 There were 4 patients at 30 milligram per kilogram
8 per week, 4 patients at 50 milligram per kilogram
9 per week, and 4 patients on placebo.
10 With only 4 patients per arm, there were too
11 few to learn much about dose response, and that was
12 a question that came up earlier. And in truth,
13 really there's too few to learn anything about dose
14 response. Dystrophin was measured at week 12, as
15 in study 28, and also at weeks 24 and 48. As
16 mentioned by Dr. Rao, these three time points are
17 referred to as the first three biopsies.
18 The study 201/202 investigators reported
19 that dystrophin increased at week 24 but not at
20 week 12. This was different than study 28, which
21 has been mentioned before, in which robust
22 dystrophin expression was reported at week 12.

1 Consistency of findings is something that we're
2 going to talk a lot about in these first few
3 slides, and that's a great concern in all areas of
4 science, including drug development.
5 I think the issue is that without
6 consistency of findings, it's really hard to know
7 if something's true, if just the basic numbers that
8 we're looking at are true. So one of the things
9 that drives the FDA standards is trying to find
10 something that's true, a number that's true, an
11 estimate of dystrophin expression that's true. And
12 the results need to be consistent to know if that's
13 really a true number that you're looking at.
14 In study 201/202, by week 48, dystrophin
15 levels of 25 to 50 percent or higher were reported
16 in all patients. These published findings seemed
17 highly encouraging, and helped lead the DMD
18 community to the conclusion that eteplirsen was
19 effective and to an understandable reluctance to
20 participate in future placebo-controlled studies.
21 This essentially marked the end of phase 1 and 2
22 studies for eteplirsen.

1 FDA learned more about the data in
2 discussions with the applicant about NDA filing and
3 became concerned about the reliability and
4 consistency of the data, communicating this clearly
5 to the applicant. FDA nevertheless agreed to file
6 the NDA based on assertions by the applicant and
7 many DMD experts, of both high levels of dystrophin
8 expression and clear clinical stabilization in the
9 12 eteplirsen treated patients.
10 FDA worked with the applicant on more
11 reliable dystrophin assays as described by Dr. Rao.
12 The applicant obtained a fourth muscle biopsy at
13 week 180 of eteplirsen treatment from 11 of the 12
14 original patients, and as the NDA was being
15 submitted, studied these biopsies with the more
16 reliable dystrophin assays.
17 In the meantime, detailed review of the
18 study 28 and first three biopsy of study 201/202
19 findings confirmed FDA's concern that the earlier
20 dystrophin assays were not reliable. For example,
21 as described by Dr. Rao, Western blot bands were
22 oversaturated. Also, regarding dystrophin positive

1 fibers, immunofluorescence images were captured and
2 read in a way that might have been overly
3 subjective with preferential selection of brighter
4 staining muscle regions.
5 Now, I'd like to shift though to the way
6 that these dystrophin staining images were
7 captured. Because dystrophin staining fades, only
8 one set of images could be captured from the
9 stained tissue. So there was an independent
10 blinded rereading of the images that were taken,
11 but the issue is how the original images were
12 taken.
13 So the independent blinded rereading can get
14 rid of bias from the reading, but it can't get rid
15 of bias in the way that the images were originally
16 selected. And that's one of the things that we're
17 concerned about because the original images were
18 not selected in a way that was more or less fully
19 automated that would allow for unbiased selection
20 of images.
21 One other point that came up was, Dr. Rao
22 had said, that it's not possible to tell the

1 difference between revertant fibers and
2 drug-induced dystrophin. And one of the issues
3 that came up in the question and answer with the
4 sponsor was talking about dystrophin associated
5 proteins. And it's true that if there's dystrophin
6 associated proteins in those fibers, that provides
7 reassurance that the dystrophin is functional. But
8 the issue is that if there's preferential selection
9 of revertant fibers, you'll also see the dystrophin
10 associated proteins.
11 So that can tell you something about the
12 exon skipped dystrophin working, but if you select,
13 preferentially select the revertant fibers, it
14 can't tell you if the drug is doing that or if
15 that's what was present at baseline.
16 So this is the fourth biopsy results, and
17 it's one of the most important slides that we're
18 going to be looking at today. Instead of the
19 expected 25 to 50 percent normal dystrophin, as was
20 mentioned before, there was only 0.93 plus or minus
21 0.84 percent of normal dystrophin in the treated
22 patients. This was measured by Western blot, the

1 most accurate method of quantification used by the
2 applicant.
3 It seems concerning that the fourth biopsy
4 result was so inconsistent with earlier results,
5 and this appears to raise additional important
6 questions and to highlight the need for independent
7 confirmation of findings. The fourth biopsy result
8 was based on one group of patients at one
9 investigative site. No matter how many times a
10 single set of data is reanalyzed, including by
11 independent readers, it does not constitute
12 independent confirmation of findings. It's still
13 just one experiment.
14 One of the critical questions today is
15 whether eteplirsen produced dystrophin. A
16 dystrophin level of about 0.1 percent was reported
17 in the controls for the fourth biopsy. It's
18 important to highlight, however, that because of
19 the lower limit of reliable detection of the assay
20 was 0.25 percent, it would be more accurate to view
21 the level in these controls as something like less
22 than 0.25 percent.

1 The reason that I'm spending some time on
2 this is that if one were to compute ratios about
3 how much dystrophin increased, you'd really want to
4 think about the lower level of detection of the
5 assay. So the levels in the control patients was
6 not accurately determined to be 0.08 percent. All
7 that we really know is that it's something -- if it
8 was zero, it might be anything between slightly
9 less than 0.25 percent and whatever number was
10 measured. We just don't know that information
11 because of the assay.
12 The dystrophin level in the controls was
13 still, even given what I said, lower than the
14 1 percent in the eteplirsen treated patients. But
15 as discussed by Dr. Rao, the controls were not
16 matched. The tissue came from different patients
17 and different muscle groups such that there is
18 concern that the comparison may be apples to
19 oranges.
20 It was mentioned before that there isn't
21 evidence that dystrophin levels are different in
22 the different muscle groups that were used, but I'm

1 not quite sure if that's the right question to ask.
2 When the applicant first identified using controls
3 from a different muscle group, we raised concern
4 about that. And normally when controls are used,
5 you try to match the controls.
6 So we advised the sponsor at that time that
7 unless there was a substantial change in
8 dystrophin, it would be confounded by using this
9 different muscle group. And as it happens,
10 different muscles do progress differently in
11 muscular dystrophy, so some muscles degenerate more
12 quickly and some more slowly. And the relative
13 amount of dystrophin in different muscle groups is
14 not well-characterized. So there's certainly
15 reason to be concerned that this was not an
16 appropriate control to pick.
17 But I think the thing that we need to focus
18 on, too, is how little the difference is between
19 the controls and the eteplirsen treated patients.
20 So we're talking about something in absolute terms
21 of less than a 1 percent difference, and that might
22 get lost when talking about the ratios.

1 How different were the controls in the
2 treated patients? Well, we know it's less than
3 1 percent in absolute terms, so that leaves, I
4 think, some question about how similar those
5 controls were.
6 So as a result, there appears to be
7 uncertainty about how much or perhaps even if any
8 of the 0.93 percent dystrophin in treated patients
9 at week 180 might have been from an effect of
10 eteplirsen versus how much might have been present
11 at baseline.
12 Again, it should be stressed that we don't
13 have Western blot data from 9 of these 11 patients
14 prior to treatment, so it's really not possible to
15 assess the change in dystrophin in these patients.
16 Now, let's shift to discussion of percent
17 dystrophin positive fibers, as determined by
18 immunofluorescence. This was the other principle
19 way that dystrophin was assessed by the applicant.
20 First, as discussed by Dr. Rao, percent
21 positive fibers is not a helpful measure of the
22 amount of dystrophin because a positive fiber does

1 not mean a normal amount of dystrophin, a
2 functional amount, or really any specific amount of
3 dystrophin. It only means an intensity judged by
4 eye to be above background of the image.
5 One of the numbers that came up before, too,
6 was greater than 30 percent of staining, but that's
7 not a measure of intensity. It's not greater than
8 30 percent of normal intensity. That's greater
9 than one-third of the circle of the muscle fiber
10 having some detectable amount of dystrophin. So
11 that's something that's just an intensity judged by
12 the eye to be above background of the image, but
13 only in a fraction of the muscle fiber. So
14 two-thirds of the muscle fiber might have no
15 detectable dystrophin staining.
16 In the fourth biopsy, the applicant reported
17 10 percent positive fibers in the eteplirsen
18 treated patients and 1 percent in the controls.
19 These were the same samples used for Western blot,
20 so similarly it's uncertain how much of this
21 difference might have been from an effect of the
22 drug versus other differences between the samples.

1 As you'll see, it also remains difficult to find
2 consistency in the percent positive fiber counts,
3 even with the improved method with three blinded
4 readers.
5 Here are the results showing percent
6 positive fibers from the muscle biopsies. The
7 results on the left were analyzed by a single
8 reader at Nationwide Children's Hospital. They
9 were read at baseline, week 12, week 24, and week
10 48. On the right are the rereads from 3 blinded
11 readers shown in blue, at the same time points,
12 week 12, 24 and 48, and then there's also a reading
13 at week 180 of eteplirsen treatment.
14 In the first three biopsies, the results
15 from the 3 blinded readers found far fewer positive
16 fibers than the original reading, shown in the gray
17 rectangle. So for example, 70 percent here,
18 23 percent here, and on down the line, 58 percent
19 versus 9 percent.
20 Percent positive fibers, there was
21 discussion about when dystrophin was produced by
22 eteplirsen, and we've been talking about maybe at

1 week 12, maybe not at week 12. But actually at
2 week 24, there weren't consistent findings either.
3 So percent positive fibers did not consistently
4 increase at week 24, even within study 201/202.
5 The numbers of patients here are small, but
6 whereas the results in the blue squares for the
7 patients started on 30 milligram per kilogram per
8 week, they do show an increase at 24 weeks of
9 treatment that wasn't seen in patients who were
10 started on placebo and switched to 30 milligram, or
11 who were started on placebo and switched to
12 50 milligram per kilogram per week.
13 So these patients were treated initially
14 with placebo for a 24-week period, but then they
15 were treated with eteplirsen for an additional
16 24 weeks. So if it was going to be a consistent
17 result, you should see the same kind of increase in
18 the second 24-week period that you saw in this
19 first 24-week period, but the dystrophin positive
20 fibers in fact for these other two groups of
21 patients don't increase at 24 weeks.
22 The fourth biopsy controls that were

1 selected by the applicant had 1 percent dystrophin
2 positive fibers. This is compared to 10 to
3 15 percent dystrophin positive fibers in the
4 original matched controls, as shown by the black
5 rectangle. So that seems like a big difference,
6 1 percent versus 15 percent, and this is in two
7 different sets of controls.
8 That seems to raise some questions, where
9 did that inconsistency come from? Was it
10 differences in the methods, or in the reading, or
11 one thing that we're worried about is it's a
12 difference between the controls, between the
13 original controls from those patients and the later
14 controls that weren't matched?
15 So there's the same kind of concern with
16 comparison of the week 180 samples and the
17 baseline. So, of course, you'd expect and hope to
18 see a substantial difference in the percent
19 positive fibers of the biopsies treated for
20 180 weeks versus those at baseline. But instead,
21 in the same baseline samples had levels -- or had
22 dystrophin positive fibers of roughly 10 to 15

1 percent, whereas the 180 week samples had
2 17 percent positive fibers. So that seems like no
3 difference or very little difference.
4 So let me just summarize the dystrophin
5 findings. There was 0.93 percent of normal
6 dystrophin as measured by Western blot after
7 long-term treatment with eteplirsen with 17 percent
8 of muscle fibers with at least some detectable
9 amount of dystrophin.
10 Because of poorly matched controls, the
11 proportion of the dystrophin produced by eteplirsen
12 as opposed to the dystrophin present at baseline
13 seems uncertain. Thus, it's not clear how much or
14 perhaps even whether these values represent an
15 increase over the dystrophin levels that were
16 present at baseline.
17 Consistency of findings is key in drug
18 development, but there is no independent
19 confirmation of these findings. The week 180
20 findings appear to be strikingly inconsistent with
21 earlier reports.
22 Ratios of dystrophin levels in treated

1 compared to control tissue that have been presented
2 by the applicant may be apples to oranges
3 comparison because of poorly matched controls. The
4 ratios also lack reliability because of small and
5 questionably calculate denominators.
6 As Dr. Rao explained, FDA is very interested
7 in drugs that might restore dystrophin, and
8 dystrophin could serve as a surrogate endpoint for
9 accelerated approval. I think as pointed out by
10 many speakers today, there's a lot of interest in
11 the relationship between dystrophin levels and
12 clinical course, and there are many publications in
13 this area, but it's important to understand that
14 when discussing very low levels of dystrophin,
15 literature reports are not always accurate.
16 The reports might state that a patient
17 expressed no dystrophin or only trace dystrophin,
18 but this may only mean that the patient had less
19 than some often poorly defined lower limit of
20 detection of the assay. In addition, reports may
21 not be precise in describing low levels of
22 dystrophin. Trace dystrophin levels are often

1 detected, but trace is not a defined or useful
2 measure of amount of dystrophin.
3 So the FDA has relied heavily on what
4 experts have written in the past about the
5 association between dystrophin and a decline in
6 progression in muscular dystrophy, and that's what
7 a lot of this information is taken from, what the
8 experts have said. So with the most reliable
9 Western blot methods, it appears that dystrophin
10 levels less than about 3 percent of normal would in
11 most patients be associated with the typical DMD
12 phenotype.
13 You may hear today, and have already heard
14 today, that DMD is milder at the high versus low
15 end of this range, and FDA can't stress enough that
16 we're open to evidence that shows this. But from
17 our review, and really from what the experts have
18 said in the past, there appears to be little
19 reliable evidence that DMD is milder at the high
20 versus low end of the range between zero and about
21 3 percent of normal.
22 There does appear to be some evidence that

1 levels need to be higher. DMD experts previously
2 suggested the need for perhaps 10 percent or higher
3 levels of dystrophin, with expression in most
4 muscle fibers, to predict a milder than average DMD
5 clinical course.
6 Let me just switch to one slide, to
7 slide 141. So it was brought up that -- so this
8 data is actually immunofluorescence data, and I
9 hadn't intended to show it at first. What we're
10 really looking for, what really allows comparison
11 of different patients to each other, and especially
12 across different studies, we're looking for Western
13 blot data, and that has an internal standard, a
14 dilution standard. It still might be cross-study
15 comparisons, but it allows some sort of more
16 reliable comparison.
17 So this data here is taken from Anthony.
18 This is the paper that the applicant cited with
19 exon 44. And I think what's striking here, and I
20 think this is the big question, the big question
21 when we're talking about the correlation between
22 dystrophin levels and the rate of decline in DMD.

1 And that is the correlation. It's taking a look at
2 which patients are doing well, which patients are
3 doing less well, and how much dystrophin is in each
4 of those 2 groups of patients.
5 So I'm not really sure how reliable this
6 data is, and it is immunofluorescence data, but one
7 of the things to take a look at is the amount of
8 dystrophin in patients that are doing well. This
9 is patient 3 from that paper. And by
10 immunofluorescence, the dystrophin level was
11 getting close to 50 percent, and then patient 4 and
12 5.
13 So patient 3 had a Becker phenotype.
14 Patient 4 and 5 were exon 44 skippable patients,
15 and they lost ambulation at 11 or 12 years old.
16 And then patient 1 and 2 had lower levels of
17 dystrophin and were still able to walk. So at
18 these low levels in patient 1, 2, 4 and 5, there
19 seems to be kind of an opposite relationship
20 between dystrophin levels and walking.
21 Then, what I really want to point to,
22 though, what I think really merits the attention,

1 is that there's really a concern that patients who
2 are doing substantially better, they have higher
3 dystrophin levels. And that's why it's important
4 to take a look at the details. That's why just
5 saying that exon 44 patients do better doesn't
6 really tell you how much dystrophin is needed for a
7 less severe phenotype.
8 I think also when we need to keep in mind
9 some of the things that were discussed more in the
10 memo, in the FDA memo, and that is that -- I mean,
11 certainly we don't want to be too pessimistic about
12 dystrophin that might lead to clinical benefit, but
13 we really do need --
14 (Laughter.)
15 DR. FARKAS: I appreciate that laughter and
16 I -- actually I want to interrupt myself to say
17 that, really, what I'm trying to do is -- what I
18 feel like I'm trying to do is set the record
19 straight, and try to explain to people the way that
20 we see the data and some of the things that we're
21 not real happy about, the way that the data is
22 often presented, and some of the things that we're

1 not really able to say to people.
2 So I think that there's also a risk in
3 comparing exon 44 patients to exon 51 patients.
4 There is a lengthy literature in Becker muscular
5 dystrophy about how the mutation really matters.
6 And the fact that exon 44 and exon 51 are close in
7 numbers, it doesn't really mean that there can't be
8 a difference in the dystrophin. And some of the
9 biggest differences are in numbers that are close
10 together. So that really doesn't tell you what's
11 going on.
12 So I wouldn't say that it makes it
13 impossible to use data from exon 44 to understand
14 how much dystrophin is necessary in exon 51
15 patients, but that needs to be considered.
16 Could we go back to slide 43? So then going
17 back to the percent dystrophin positive fibers,
18 dystrophin positive fibers, it's been mentioned
19 before, it's very sensitive to the subjective view
20 of the person reading it, and it's also sensitive
21 to the conditions of the assay.
22 So what we've seen is that in DMD, typical

1 DMD patients can have dystrophin staining anywhere
2 from zero to 100 percent of their fiber. So it's
3 not a very good method to differentiate patients
4 who are going to have a more severe course from
5 patients who are going to have a less severe
6 course.
7 But what we've seen with the 17 percent
8 number, 17 percent dystrophin positive fibers in
9 the eteplirsen treated patients, that's more
10 typical of untreated DMD. At least in the range of
11 zero to 100 percent, the 17 percent is more typical
12 of untreated DMD. And what is more typical in
13 patients with a milder course, in patients with
14 Becker muscular dystrophy, they have irregular, it
15 is irregular dystrophin staining, but that
16 irregular dystrophin staining is found in basically
17 100 percent of fibers.
18 Then there's this issue of the lowest amount
19 of dystrophin that might be associated with the
20 Becker phenotype, and that's really a problematic
21 question to answer. It's not a very helpful
22 question because the truth is that some patients do

1 well with zero dystrophin. It's that the
2 correlation between dystrophin and how patients do
3 is very real, but it's absolutely not absolute. So
4 there are rare patients with the milder Becker
5 muscular dystrophy phenotype that have dystrophin
6 levels near zero.
7 These unusual cases highlight that there is
8 often a lack of clear relationship between
9 dystrophin levels and severity. Mild disease in
10 these individuals is likely unrelated to -- not the
11 result of trace levels of dystrophin. So this is
12 an active area of research, a very important area
13 of research, but it's really unrelated to the
14 proposed mechanism of action for eteplirsen.
15 These half-brothers just demonstrate this
16 point. They have the same mutation, but their
17 disease course is very different. Both
18 half-brothers are dystrophin negative, except for
19 revertant fibers. So again, this idea of trying to
20 find the correlation between revertant fibers and
21 how well patients do, there's been a lot of
22 interest in that, but there hasn't really been much

1 ability to find that kind of correlation.
2 The younger half-brother become wheelchair
3 bound at age 9. The older half-brother remained
4 walking until age 15, walking well still at age 15.
5 Although these cases are rare, it illustrates the
6 complex relationship between dystrophin, other
7 genes, and clinical course.
8 Now, I'm going to switch to talking about
9 the clinical data, starting with the 24-week
10 placebo-controlled period of study 201/202. As
11 described earlier, study 201/202 was planned as a
12 24-week placebo-controlled trial in 12 patients,
13 randomized to either eteplirsen 50 milligram per
14 kilogram per week, eteplirsen 30 milligram per
15 kilogram per week, or placebo. Each group had 4
16 patients.
17 The primary endpoint was dystrophin
18 expression, but multiple clinical endpoints were
19 also measured, including 6-minute walk test, the
20 North Star Ambulatory Assessment.
21 The prespecified clinical endpoints of
22 study 201 at week 24 and study 202 at week 48 were

1 negative. The applicant performed a post hoc
2 analysis based on a number of major changes,
3 including removing two patients treated with
4 eteplirsen who deteriorated rapidly, and picking a
5 time point to analyze that was outside the control
6 trial period.
7 FDA explained that these types of changes
8 did not appear reasonable, even for hypothesis
9 generation, and that the post hoc analyses were not
10 interpretable. However, the applicant announced
11 the post hoc results generating considerable public
12 attention.
13 Now, let's consider the clinical data from
14 long-term open-label treatment with eteplirsen in
15 study 201/202. As others from FDA will also stress
16 today, it's important to make clear that FDA
17 consistently and strongly encouraged the applicant
18 to perform an adequately powered, randomized,
19 double-blind, controlled trial, and expressed
20 strong doubts regarding the interpretability of
21 comparisons of patients in study 201/202 to
22 external controls.

1 I should add that we gave that advice when
2 we already saw how patients were progressing, so we
3 were open. We are open to data that could be -- we
4 are open to an effect that could be large enough to
5 be interpretable in a historically controlled
6 trial. But what we saw that that didn't seem to be
7 occurring, we gave very strong and very consistent
8 advice to the applicant that we didn't think this
9 was going to lead to an interpretable comparison to
10 historical controls. So again, as I mentioned, FDA
11 is receptive to interpretable data from externally
12 controlled trials.
13 FDA also explained to the applicant that
14 data from externally controlled trials in DMD may
15 only be interpretable if a relevant objective
16 endpoint, obviously insulated from bias,
17 demonstrated compelling data that were clearly
18 outside the known variability range for DMD. And
19 I'm going to spend quite a lot of time talking
20 about the amount of effect that can be introduced
21 by endpoints that are partially subjective.
22 So FDA's advice has been entirely consistent

1 with what is known about externally controlled
2 trials, including in muscular dystrophies. DMD
3 experts, and we have been looking at the advice of
4 DMD experts, have noted that physical function may
5 be affected by simply being in an efficacy study.
6 Patients outside of efficacy studies can perform
7 worse for reasons that are not well understood.
8 This example is from studies of
9 facioscapulohumeral muscular dystrophy. The
10 investigators wrote, "Whereas natural history data
11 showed a decrease in strength over one year, there
12 was in the efficacy studies an apparent increase in
13 strength in both the placebo and treatment groups."
14 So this is the kind of difference, the
15 difference of an increase versus a decrease. It's
16 a binary difference, and even that can occur when
17 comparing patients who are in a drug trial to
18 patients who are in a natural history cohort.
19 The DMD experts went on to say, "Patients in
20 clinical trials in FSHD may have better outcomes
21 than those in natural history studies regardless of
22 treatment assignment, emphasizing the importance of

1 placebo groups."
2 The observations of DMD experts also guided
3 FDA advice to the applicant that ambulation was a
4 particularly problematic endpoint in externally
5 controlled trials in DMD. This is a near quote
6 from one of the publications and from talking to
7 experts. This is because near the age at which
8 patients lose ambulation, loss of walking is not a
9 sudden hard endpoint. Preservation of ambulation
10 and other skills is affected by subjective decision
11 making from families and caregivers about those
12 skills, with such factors as risk of falls and
13 injury from continued ambulation weighed against
14 the safety and speed of allowing patients to use a
15 wheelchair.
16 It was mentioned before that recovery of
17 walking after a fracture might be an indication of
18 efficacy. And we've taken a look at this, but
19 there are other ways to look at that same kind of
20 data. People or patients who experience fractures,
21 that might mark a reasonable time, based on
22 clinical judgment, for that patient not to walk

1 because they got a fracture.
2 So there are a lot of decisions that need to
3 be made, too. It's not just a fracture leads to
4 loss of ambulation. It's really a fracture leads
5 to a series of clinical decisions about what to do.
6 And concern about a fracture leads to a series of
7 clinical decisions about what to do.
8 I see some heads shaking out there. This is
9 the advice that we see, the information that we see
10 in publications, people trying very hard to try to
11 get kids walking again after they have a fracture,
12 and that seems to be something that's possible to
13 do in many cases, not all, if one's mind is set on
14 it.
15 In a randomized controlled study, the only
16 major difference between the treatment groups is
17 the presence or absence of the drug. In contrast,
18 for an externally controlled trial, there are
19 potentially many differences, both known and
20 unknown, between drug treated patients and
21 controls.
22 To understand if there's evidence of drug

1 efficacy in an externally controlled trial, it's
2 absolutely necessary to study the sources and
3 possible sizes of non-drug related differences
4 between groups. A few examples of non-drug related
5 differences between the study arms in study 201/202
6 follow, and others are described in the FDA memos.
7 I should just add that looking for these
8 differences, that's just absolutely critical to try
9 to understand if drugs work or not. It's not
10 something that the FDA could avoid doing. It's
11 something that we need to look into.
12 So first, interpretability of externally
13 controlled trials -- for an interpretable
14 externally controlled trial, it's necessary that
15 efficacy endpoints be assessed the same way in the
16 groups being compared. So that's fairly obvious,
17 the things that are being compared have to be
18 similar to each other. They have to be measured
19 similarly to each other for a fair comparison.
20 One reason that 6-minute walk test is
21 problematic is that the decision to ask a patient
22 to attempt to perform the test, to attempt to do

1 6-minute walk test, versus deeming the patient
2 unable, is based partially on judgments and
3 attitudes of the investigator, patients, and
4 caregivers. Moreover, the distance walked could
5 depend on motivation and cooperation.
6 The FDA's concerned that there may have been
7 important differences in how such decisions were
8 made for eteplirsen treated patients compared to
9 external controls. And this is something that came
10 up in the applicant's discussion earlier. I'd just
11 like to talk a little bit more in detail about it.
12 So I'm going to focus on two specific
13 patients, but it's important to understand that the
14 issue of endpoints being assessed differently is
15 not limited to these two patients. It's just that
16 there is more evidence of a difference for these
17 two patients.
18 Two of the 13 control patients selected by
19 the applicant were able to perform 10-meter
20 run/walk reasonably well but were deemed unable to
21 attempt 6-minute walk test. Data for one of these
22 patients is shown in the table.

1 So at age 10, this patient walked 10 meters
2 in 10 seconds, and walked 356 meters in 6 minutes.
3 But age 11, the patient walked 10 meters in
4 12 seconds, which is still a reasonable walking
5 ability, but was said to have lost ambulation as
6 measured by 6-minute walk test.
7 So there's been some discussion earlier
8 about how far patients might be able to walk, or if
9 patients could walk, or I think what the real
10 discussion was is that it wouldn't be unusual to
11 lose ability to do 6-minute walk test before one
12 lost the ability to do 10-meter walk/run. And I
13 think one thing to point out before I get to some
14 more of the numbers, there's not very much
15 difference between walking 10 meters in 10 seconds
16 and walking in 12 seconds.
17 So there's a 6-minute walk test. If you
18 calculate it out distance that somebody could walk
19 if they were given multiple 12-second intervals,
20 you'd think they should be able to walk something
21 more than none, if given the opportunity to attempt
22 to walk for 6 minutes, that there could be some

1 distance recorded.

2 This is also talked about a little bit more

3 in the memo, and I'd like to call up a slide that

4 was in the memo, slide 125. So this is also from

5 the Italian cohort, and there are some patients

6 here who walked 12 seconds, and then 6-minute walk

7 distance is down at the bottom.

8 So there's certainly a range of values here.

9 One patient who did 10-meter run/walk was walking

10 about 125 meters on 6-minute walk distance. But

11 there really is a whole range, so if you trace

12 12 seconds over, and then down, there's also

13 patients who did 10-meter run/walk in 12 seconds

14 who were walking more than 300 meters in 6-minute

15 walk test.

16 So that's one of the reasons that we're very

17 concerned about when patients are deemed unable to

18 do a test because when the test isn't measured, you

19 really don't have any way of knowing what distance

20 the patient would have walked.

21 Of course, too, the way that the applicant

22 is counting ambulatory versus non-ambulatory, these

1 Kaplan-Meier curves or other graphs, that's based
2 on the 6-minute walk test. So that's based on
3 deeming the patient unable to walk.
4 So that gets right back to the whole issue
5 of clinical judgment, that the patients aren't
6 expected to be able to walk, so 6-minute walk test
7 isn't attempted, so there's the conclusion that the
8 patient is no longer ambulatory.
9 Could I have slide 57? So I'd just like to
10 switch a little bit now to the impact, or possible
11 impact of differences in supportive treatment. So
12 supportive treatment, including steroids, can have
13 important effects on slowing disease decline in
14 DMD.
15 The issue that FDA would like to point out
16 is that there are some differences in the
17 supportive care received by patients in the
18 eteplirsen trial and patients from external natural
19 history studies. One example is that the
20 eteplirsen patients were treated with steroids for
21 about a year longer, and that could be important
22 for maintaining ambulation.

1 But that's not really the key point that the
2 FDA is trying to make. The key point is really
3 that small differences, seemingly small differences
4 in care that patients receive can seemingly lead to
5 larger than expected differences in the disease
6 course and in the age of loss of ambulation.
7 Can I have the next slide? So this slide
8 shows some recent observational data from the
9 Cooperative International Neuromuscular Research
10 Group, also known as CINRG. The investigators
11 compared the course of patients on different
12 steroid regimens to try to determine which might be
13 the most effective. What they concluded is that
14 seemingly small differences in patient care can
15 confound interpretation of observational data in
16 DMD.
17 This is data taken from a larger table, but
18 it shows two groups of patients who seemingly have
19 a very similar steroid treatment, deflazacort that
20 was given daily, or deflazacort that was sometimes
21 given daily or switched to every other day or some
22 other dosing regimen.

1 But the point is these patients, they're not
2 exon 51 patients, but groups of DMD patients with
3 seemingly similar care and not selected for any
4 particular mutation, that there was a two-year
5 difference in loss of ambulation between these
6 patients.
7 So based on this data, and similar data that
8 the DMD experts showed, they concluded that
9 differences in standards of care and dosing
10 complicate interpretation. This study emphasizes
11 the necessity of a randomized, blinded trial of
12 glucocorticoid regimens in DMD.
13 The eteplirsen data are similar in some
14 ways, including the small sample size. So that
15 there were just 8 patients in this group, that
16 might have led to an unstable estimate of age of
17 loss of ambulation, but there's that same kind of
18 concern in the small eteplirsen study. Thus, even
19 a two-year difference in age of loss of ambulation
20 between eteplirsen treated patients and external
21 controls may not be a drug effect.
22 There can be other perhaps less obvious

1 sources of differences between study arms that can
2 confound interpretation of externally controlled
3 studies. Patients who are not motivated, able, or
4 qualified to enroll in drug studies may remain in
5 natural history studies. So one of the things
6 that's important to consider is that drug studies
7 and natural history studies were being conducted at
8 the same time when data for these groups of
9 patients was being collected.
10 Patients who have progressed more rapidly
11 may be over-represented in natural history studies
12 if they no longer meet eligibility requirements for
13 drug studies. Again I'm going to talk about a
14 specific example, but it's important to stress that
15 this is not limited to these specific patients;
16 rather it's only that there is clearer evidence of
17 differences for some patients than for others.
18 One of the 13 eteplirsen controls lost
19 ambulation after 1 year and stayed in the
20 observational study for several years, long enough
21 to enable matching to eteplirsen patients. Two
22 other exon 51 patients had similar baseline age and

1 6-minute walk distance, but discontinued the
2 observational study to participate in drug studies,
3 and were therefore not under observation long
4 enough to potentially be controls for the
5 eteplirsen study.
6 It even goes beyond matching. They weren't
7 there for long enough to enable matching. You can
8 only do matching to patients that remained in the
9 observational study for the same amount of time
10 that patients were treated with eteplirsen. So the
11 concern is that the only patient out of these three
12 who was available to be matched to the eteplirsen
13 patients was the one who definitely had a rapid
14 decline in ambulation.
15 Here's an important point. Different
16 analysis approaches are needed for externally
17 controlled trials than for randomized,
18 double-blind, placebo-controlled trials. As just
19 discussed, in externally controlled trials, data
20 may be gathered differently from each group, and
21 groups are different in ways that are impossible to
22 fully understand or measure.

1 P-values, sensitivity analyses, the kinds of
2 evidence that we're used to looking at from
3 randomized placebo-controlled trials, they can only
4 tell you that there's a difference between the two
5 sets of numbers, but they can't tell you where that
6 difference came from.
7 So again, the important part of the
8 randomized placebo-controlled trial is it's a
9 really good way to get the two groups of patients
10 the same. You don't know all the differences, but
11 you've sorted one part of the patients to one arm,
12 one part of the patients to the other arm randomly,
13 and that takes care of most of the differences.
14 Then the p-value can be interpretable. It
15 can tell you something about the chance of seeing
16 the size difference that you might see. But when
17 you start out with patients that are different from
18 each other and where the endpoints have been
19 measured differently from each other, taking a look
20 at the p-values doesn't give you the kind of
21 information that you need.
22 The key question to ask, really, the only

1 question that can help in a situation like
2 this -- and we are open to historically controlled
3 trials at FDA. But the question that needs to be
4 asked is kind of what we're going through right
5 now, how big were the differences between the
6 patients at baseline? How many differences were
7 there during the course of the study? You have to
8 use your judgment about how big those differences
9 were. And then take a look at the difference in
10 the endpoints between the two groups of patients
11 and try to decide if it was from some of these
12 known or unknown sources of differences between the
13 patients or if you're convinced that it was from an
14 effect of the drug.
15 So now let's turn to the figure, some of the
16 figures that I showed earlier, that compare the
17 clinical data from the eteplirsen patients and
18 external controls.
19 The applicant has shown these 6-minute walk
20 test data as a function of time on study, but
21 showing by age is more meaningful because loss of
22 ambulation is correlated with age in DMD, and so

1 it's important to adjust for age.
2 The patients and controls in the study
3 varied widely by age at baseline from as young as 7
4 to as old as almost 12 years old. In the context
5 of DMD, these are very different ages. So when
6 we're talking about just the original baseline
7 matching that was done for the patients, the
8 patients were matched by quite a range, 7 to
9 12 years old, so that's not really very close
10 matching for the DMD.
11 So that's one of the problems with the way
12 the applicant's presenting the data, and what we
13 really need to do to understand the course of the
14 patients is compare patients who are of similar
15 age.
16 So in these slides, patient's age is shown
17 on the X-axis, and the 6-minute walk test is shown
18 on the Y-axis. The red lines show eteplirsen
19 patients and the blue show the applicant's external
20 controls. Each line begins at the patient's age at
21 enrollment and continues through 4 or 5 years,
22 depending on the available data.

1 As described earlier, there are many reasons
2 why there may be very real but not drug-related
3 differences between eteplirsen and control
4 patients. Differences in the way the endpoints
5 were assessed are highlighted here. Patients
6 marked with an X -- so this patient's marked with
7 an X, so those were the two patients who were
8 described on slide 56 who had 6-minute walk test
9 values of zero assigned when they could still walk
10 fairly well as measured by 10-meter run/walk.
11 The patients marked with question marks,
12 these three patients, those were patients in whom
13 6-minute walk test was assigned zero based on a
14 yes/no question, was this patient walking at year
15 4?
16 The problem is that that's comparing data
17 that was measured differently. It's simply not
18 possible to know if the value would have been the
19 same if 6-minute walk test had been measured under
20 the same careful testing procedures used for
21 eteplirsen patients, including, as brought up
22 before, that all eteplirsen patients were tested

1 twice at most visit.
2 Because of many types of non-drug related
3 differences, including the way endpoints were
4 assessed, these figures may really be apples to
5 oranges comparisons. So we're going to continue to
6 show the data that we have, but there's a great
7 deal of uncertainty in the similarity of how these
8 data were obtained, if they really represent
9 measurements of the same thing. This is important
10 to keep in mind.
11 The arrows in this figure are only there to
12 illustrate that some patients declined in 6-minute
13 walk test earlier than average, some about average,
14 and some older than average across a wide range of
15 ages.
16 Importantly for eteplirsen and control
17 patients, there appears to be a general similarity
18 in age and rate of decline. So again, if we take a
19 look at going all the way across here -- and again,
20 part of the issue of comparing these two groups of
21 patients is that the natural history patients, a
22 lot of those patients were from past history, so we

1 know the course of those patients. We know the age
2 at which they lost ambulation.
3 One of the things that we really need to
4 think about when we're making comparisons about the
5 patients who are currently walking and the patients
6 who are not currently walking is that the patients
7 who are not currently walking, they were measured
8 in some cases years ago, and the patients who are
9 still walking are at similar or younger ages, but
10 they're measured now.
11 So again, taking a look at the course of the
12 different patients, we have the age at which
13 patients are starting to decline and the general
14 course of that decline. And it really more or less
15 alternates with blue and red and blue and red
16 across most of this figure.
17 I showed this before. So it doesn't look
18 like there's this binary kind of difference in age
19 of loss of ambulation between eteplirsen treated
20 patients and historical controls.
21 There's no bigger apples to oranges
22 comparison than comparing walking in an 11-year-old

1 patient with DMD to walking in a 15-year-old with
2 DMD, but that's what is done with some of the
3 applicant's analyses. Instead we need to compare
4 eteplirsen patients to controls of similar age.
5 So the 11-year-old, marked by the arrow
6 here, appears to be progressing about the same as
7 the controls on either side. So there are blue
8 patients here, and then there's a red eteplirsen
9 patient, and blue controls here. It's simply not
10 correct to say that the 11-year-old is necessarily
11 doing better than these 15-year-olds because it's
12 confounded by age. The 11-year-old is still 11 and
13 it's hard to know what's going to happen when the
14 11-year-old becomes 15.
15 Then going along the patients, the same
16 comparison can be made for these two 12-year-old
17 patients marked by the arrows. They are
18 progressing at a rate similar to control patients,
19 and in fact for these patients the lines are
20 basically overlapping here.
21 More or less the same comparison can be made
22 for these 13 and 14-year-old patients. And it's

1 important to say again it doesn't have to be exact.
2 There's concern that the patients were measured
3 under conditions that were different. But the
4 general course of progression, even in these
5 patients, these 13 and 14-year-old patients marked
6 by the arrows, is similar to the natural history
7 patients.
8 So now for some patients, the ones in the
9 oval here, there may be differences in reported
10 6-minute walk test for eteplirsen and control
11 patients. Again, it needs to be remembered that
12 there were differences in the way that these values
13 were assessed.
14 So the FDA is certainly keen on looking at
15 the data in different ways to see if there's a
16 change in the average age of walking of patients,
17 treated patients, or to see if maybe only some
18 patients are responding in a way that could be
19 clearly attributed to drug.
20 So it's been suggested that the performance
21 of some eteplirsen patients is very different from
22 the natural history of DMD. So there are one or

1 two patients, eteplirsen treated patients, who are
2 currently walking at an age when none of the 13
3 natural history patients selected by the applicant
4 are walking.
5 But unfortunately, there's recent data that
6 suggests that this is still what can be expected
7 from natural history patients. What we have to do
8 is take a look at other groups of natural history
9 patients, and I think that's the same thing that
10 we're talking about with consistency. It's really
11 necessary when taking or trying to interpret
12 historically controlled trials, to take a look at
13 the variety of different kinds of natural history
14 experience to try to understand the variability
15 between groups.
16 DR. ALEXANDER: Dr. Farkas, I'd just like to
17 ask you to be mindful of the time as we proceed.
18 DR. FARKAS: Sure.
19 Okay, so this is the Kaplan-Meier curve that
20 we saw before. A key point is that the age of loss
21 of ambulation in exon 51 skippable patient appears
22 to be older than is sometimes realized. And that's

1 really a huge point to be made, and we've heard
2 experts talk here today, but I think the bottom
3 line, and perhaps to save time, is that we've been
4 looking at all the data that we can get about the
5 age of loss of ambulation in exon 51 skippable
6 patients. And from the CINRG data, 25 percent of
7 exon 51 boys are walking at 16 years of age, and
8 15 percent are walking at 18 years of age.
9 This I showed before, the kind of
10 interpretation that seems appropriate is to try to
11 figure out what percent of the eteplirsen patients
12 would be walking at 16 years of age.
13 Other historical data appear to be generally
14 consistent with the CINRG data. The exon 51
15 skippable patients in the placebo arms of recent
16 randomized placebo-controlled studies of
17 drisapersen that this committee talked about in
18 November, they seemed to also indicate that
19 patients can walk to 16 years of age. And then
20 that group is described more in the memo. They
21 were younger patients who still had well-preserved
22 rise times and 6-minute walk test that seemed

1 generally consistent with the Kaplan-Meier curve
2 for the CINRG patients.
3 There's also data being collected about the
4 natural history of muscular dystrophy from the MD
5 STARnet program of the Centers for Disease Control
6 and Prevention. And I'll skip over some of this
7 data, but we can refer to it later if we need to.
8 But the key thing from this data is that
9 there were 26 exon 51 patients identified, and out
10 of those 26 patients, 3 patients were walking at or
11 beyond 14 years, and 2 of these 3 patients were
12 walking at or beyond 16 years. And also out of
13 these 26 patients, there's still 15 who are still
14 ambulant. So the number of these patients who
15 might ultimately be found to be walking past age 14
16 or age 16 might be more than that.
17 So we were talking about correlation between
18 dystrophin levels and change in 6-minute walk test.
19 This is just an exploratory analysis done by the
20 FDA. There's change in 6-minute walk test found
21 versus dystrophin expression, and we didn't see a
22 correlation. And this is a very small data set,

1 but this is the kind of data that if you saw a
2 correlation, that's the kind of correlation you'd
3 like to see, to understand if there was a
4 difference in the small amounts of dystrophin that
5 we see, that we might see.
6 So other functional endpoints can be very
7 important. NSAA may be a particularly important
8 measure of disease progression in DMD because it
9 measures the number of underlying abilities related
10 to muscle strength and to safe and practical
11 walking. And in the eteplirsen study, it may be a
12 more reliable measure than 6-minute walk test
13 because it was more consistently measured, with
14 fewer, although some instances of zero being
15 assigned without the measurement being conducted.
16 So the arrow here indicates what appears to
17 be a generally similar slope of decline for both
18 treated and control patients. You'll notice that
19 more control patients are to the left of the
20 figure, but that's because of lower mean baseline
21 scores in the controls. So that itself is
22 something important to take a look at.

1 On this slide, we did take a look at the
2 NSAA score by years on treatment, and you can see
3 that there's a baseline imbalance between the two
4 groups of patients, with the control patients a
5 little bit lower on the NSAA score at baseline.
6 And this is one of the kinds of differences that
7 could also lead to the control patients not doing
8 as well over the course of the study.
9 So this slide is a little bit complicated,
10 but it takes a closer look at, again, the FDA also
11 trying to figure out are there some
12 patients -- patients who are the oldest that are
13 doing the best, are there some patients who might
14 suggest that the course of decline in the treated
15 patients is less than could be expected by natural
16 history.
17 I think that the main point of this is that
18 there's a similar decline in NSAA score and a
19 fairly dramatic decline in NSAA score even for the
20 patients who were walking relatively well. So the
21 NSAA score in these patients is down at 10 or 9 or
22 so, and that indicates a substantial loss of

1 walking ability.
2 So even though at this time, the 6-minute
3 walk test is relatively well preserved versus other
4 patients, there's really no clear indication that
5 these patients would continue walking beyond the
6 known natural history of exon 51 patients.
7 Ability to rise from the floor may be
8 another useful measure of disease progression in
9 DMD. Lower values indicate a better score and more
10 horizontal course indicates slower progression. So
11 it's notable that two of the patients with the most
12 preserved rise time at older ages were historical
13 controls.
14 This graph also shows how it looks like
15 there may be a difference in how endpoints were
16 assessed for eteplirsen patients versus external
17 controls. Six of the eteplirsen patients have rise
18 time values of more than 25 seconds, just these
19 patients here, whereas none of the controls have a
20 value larger than 25 seconds, and that's delineated
21 by the dotted line.
22 We can't know why there was this difference

1 in the maximum values measured. The protocols and
2 case report forms from the Italian and Belgium
3 studies were very brief and don't provide details
4 about that. But we do know that in a different
5 natural history study, in the CINRG study,
6 25 seconds is indicated in the protocol as a time
7 beyond which testing of some endpoints might not be
8 considered.
9 FDA recently received data, additional data
10 from the CINRG study for 10-meter run/walk, rise
11 time, and 4-step climb. FDA is still in the
12 process of analyzing this data but would like to
13 present some initial observations.
14 Prior to the receipt of the data, the FDA
15 made a prespecified plan for the matching, so that
16 it will be a fair matching not based on FDA looking
17 at the data. And that was based on exon 51
18 skippable, ambulatory at baseline, baseline age 6
19 to 12 years, and 10-meter run/walk time less than
20 10 seconds. 10-meter run/walk was considered the
21 primary comparison because there wasn't much
22 6-minute walk test data currently available in the

1 CINRG database.
2 So here, the 10-meter run/walk time is shown
3 on the Y-axis, and age is shown on the X-axis.
4 Lower values indicate better performance. The red
5 lines show the course of eteplirsen patients, and
6 the blue lines show the course of the CINRG
7 controls. The lines show the results for the
8 10-meter run/walk test that were actually
9 attempted, not deemed as unable. And the circles
10 at the ends of these lines, those indicate patients
11 in whom the next value was imputed as unable.
12 The course of 10-meter run/walk appears to
13 be similar for eteplirsen treated and CINRG
14 patients. You can see many CINRG patients tracking
15 with the eteplirsen patients, including the
16 patients who did best was a CINRG patient. But
17 there's a wide range of different courses, but
18 basically overlap of the red and blue lines.
19 Again, eteplirsen patients were measured the
20 higher values, but this may reflect a difference in
21 when patients who were deemed unable to attempt the
22 endpoint. And there are patients from the CINRG

1 study that had the best preserved function on
2 10-meter run/walk.
3 Now, we're looking at rise time, and the
4 course of rise time also appears to be similar for
5 eteplirsen treated and CINRG patients for values
6 that were measured. The CINRG patients looked much
7 like the external controls from Italy and Belgium
8 also that were shown in slides 88 and 89. Note
9 that none of the CINRG patients are attempting the
10 test once the rise time reaches 20 to 25 seconds.
11 And this is the course of 4-step climb, which also
12 appears to be similar for eteplirsen treated and
13 CINRG patients for values that were measured.
14 I'd like to move on to, again, conclusions.
15 And I know that I've tried to explain things
16 quickly and I think shown clearly that I think you
17 haven't heard the whole story, for many years that
18 you haven't heard the whole story.
19 But I really do want to reassure everybody
20 that I remain open to what we hear from the
21 community, and I remain open from what we hear from
22 the applicant. And I've made no final decision and

1 nobody else on the review team has made any final
2 decisions about what they think about the data.
3 From the placebo-controlled portion of
4 study 201/202, including from the applicant's
5 post hoc analyses, there does not appear to be any
6 evidence of efficacy for eteplirsen.
7 Interpretation of the externally controlled portion
8 of study 201/202 must keep in mind the limitations
9 of an externally controlled study, which are well
10 known and detailed in FDA guidance and
11 international guidelines, such as ICH E-10.
12 Based on an assessment of all the physical
13 performance measures, disease progression appeared
14 to be similar for eteplirsen treated patients and
15 external controls. All eteplirsen patients who
16 have maintained ambulation are still well within
17 the age range in which exon 51 skippable patients
18 appear commonly to walk.
19 It does not appear possible to conclude that
20 differences in physical performance between
21 eteplirsen treated patients and external controls
22 resulted from an effect of eteplirsen instead of

1 from other differences and influences, both known
2 and unknown, between the groups, both at baseline
3 and during conduct of the study.
4 Regarding general drug development
5 considerations, this is very important. It's
6 really one of the most important slides here
7 because what we have to remember is that we're
8 developing these drugs -- we need to develop these
9 drugs as thoroughly, as effectively, as efficiently
10 as possible. Dose limiting toxicity from
11 eteplirsen was not observed at the doses studied.
12 Higher doses and more frequent dosing could hold
13 promise for the future. Thank you.
14 So I'd like to introduce Dr. Bastings,
15 the --
16 DR. ALEXANDER: I think we'll wait actually
17 for that, but thank you very much for your
18 presentation.
19 DR. FARKAS: Thanks.
20 DR. ALEXANDER: So I'd like to suggest that
21 we break for lunch, and then when we resume after a
22 45-minute break, we'll hear from Dr. Bastings, as

1 well as have an opportunity for clarifying
2 questions for the FDA.
3 So we'll return at 12:45. I'm sorry. We'll
4 return at 1:45. Please take any personal
5 belongings you may want with you at this time. And
6 committee members, please remember that there
7 should be no discussion of the meeting during lunch
8 amongst yourselves, with the press, or with any
9 member of the audience. Thank you very much.
10 (Whereupon, at 12:57 p.m., a lunch recess
11 was taken.)
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1 A F T E R N O O N S E S S I O N

2 (1:48 p.m.)

3 DR. ALEXANDER: We're going to begin with

4 the afternoon portion of the committee. Thank you

5 very much, and welcome back.

6 So we'll continue where we left off with

7 concluding remarks from the FDA. I'd like to ask

8 Dr. Eric Bastings to come to the podium.

9 **FDA Presentation - Eric Bastings**

10 DR. BASTINGS: Good afternoon. My name is

11 Dr. Eric Bastings. I am deputy director of the

12 Division of Neurology Products. Duchenne muscular

13 dystrophy is a serious and devastating disease with

14 profound unmet medical need and no approved

15 treatment.

16 Great hope was raised by early reports by

17 the applicant that with eteplirsen treatment,

18 dystrophin numbers were increased to levels as high

19 as 50 percent of normal and that the course of the

20 disease had stabilized, effects which would have

21 been unprecedented for Duchenne muscular dystrophy.

22 FDA provided extensive discussions and

1 guidance during the eteplirsen development program.
2 Just between 2013 and 2015, FDA held 13 formal
3 meetings with the applicant about eteplirsen. As
4 was discussed earlier by Dr. Rao and Dr. Farkas,
5 FDA identified significant methodological concerns
6 about the biomarker assessment and provided
7 extensive guidance on methods for collection of
8 additional biomarker data. Eteplirsen's
9 development program also benefited from extensive
10 involvement and guidance from senior FDA
11 management.
12 Study 201/202 was also the object of
13 extensive discussions. After study 201 did not
14 meet its primary clinical endpoint, and as FDA did
15 not consider the post hoc analyses conducted by the
16 applicant to be scientifically valid, FDA advised
17 the applicant to conduct an adequately controlled,
18 adequately powered, randomized placebo-controlled
19 trial to assess the clinical benefit of eteplirsen.
20 At the time, the company heard the view that
21 a placebo-controlled trial would not be feasible,
22 that few, if any patients, would be willing to

1 participate in a second placebo-controlled trial
2 because they already felt so strongly that
3 eteplirsen was effective. This was an unfortunate
4 situation.
5 The publication of the results of study 201
6 may have led to this perception. It stated that
7 after 48 weeks of eteplirsen treatment, 52 percent
8 of muscle fibers seemed positive for dystrophin,
9 and that 6-minute walk distance was augmented by
10 67 meters.
11 Unfortunately, as explained by Dr. Rao and
12 Dr. Farkas this morning, there were problems with
13 these conclusions. In any case, the applicant
14 instead elected to continue open-label
15 administration of a eteplirsen in study 202, which
16 has now been ongoing for over four years and is
17 proposing approval primarily based on the post hoc
18 comparisons of patients in study 201/202 to an
19 external control.
20 Many of you may be wondering why the public
21 is only hearing now about such extensive FDA
22 concerns about eteplirsen and why only after the

1 NDA has been submitted. Because of laws governing
2 trade secret, FDA is generally unable to provide
3 any information to the public about its finding
4 regarding drugs under development and is unable to
5 comment about information provided by the drug
6 developer.
7 Because of those restrictions, some
8 decisions or positions taken by the FDA, or FDA's
9 silence, might be construed by the public and the
10 patient community as a lack of caring, a lack of
11 understanding, or a lack of expertise when they
12 simply reflect a legal restriction against sharing
13 commercial confidential information with the
14 public.
15 Advisory committee meetings, such as today,
16 provide a unique opportunity for FDA to discuss
17 with a panel of advisors developer data and FDA
18 views on these data, and we very much look forward
19 to hearing from the committee later this afternoon.
20 I would now like to briefly review with you
21 the evidence that was provided this morning and
22 discuss why we came to very different conclusions

1 than those of the applicant. So let's start with
2 the biomarker evidence.
3 We agree that there is evidence of
4 production of exon 51 skipped mRNA with eteplirsen
5 treatment, supporting its proposed mechanism of
6 action. The method, however, does not show how
7 much RNA was produced or whether this mRNA led to
8 production of dystrophin.
9 After 3 and a half years of treatment, the
10 proportion of muscle fibers with detectable
11 dystrophin, identified by immunofluorescence, was
12 17 percent of normal plus or minus 10 percent. As
13 was discussed by Dr. Farkas, it is not clear
14 whether 17 percent constitutes an increase from
15 baseline. Also, as discussed by Dr. Rao, this
16 method is most useful for showing location of
17 dystrophin in the muscle and has major shortcomings
18 for quantifying dystrophin.
19 Therefore, we believe that the most relevant
20 measure of dystrophin for you to consider is the
21 amount assessed by Western blot. That amount after
22 3 and a half years of treatment is 0.9 percent of

1 normal, plus or minus 0.8 percent. That number,
2 which became only known to FDA after the NDA had
3 been submitted, is very disappointing and far lower
4 than estimates presented earlier by the applicant.
5 The biomarker data are important for the
6 committee to consider. As you've heard, if we
7 believe that the biomarker data are reasonably
8 likely to predict clinical benefit, it would open
9 up the prospect of accelerated approval.
10 There are two parts to this question.
11 First, is there adequate evidence that eteplirsen
12 produced dystrophin? And second, was the amount
13 produced reasonably likely to predict clinical
14 benefit?
15 There are some aspects of the data that can
16 be considered that if positive would support the
17 reasonably likely question. If there were a
18 correlation between the amount of dystrophin
19 detected in the muscles of individual boys, and
20 preservation of their physical abilities, such a
21 link would help support the concept that the amount
22 of dystrophin detected was reasonably likely to

1 predict clinical benefit. So let's briefly discuss
2 an exploratory analysis FDA conducted.
3 In the figure, which was shown on
4 Dr. Farkas' slide 80, the amount of dystrophin as
5 measured by Western blot is shown on the X-axis,
6 and the change in 6-minute walk distance is shown
7 on the Y-axis. For the 4 patients with the best
8 preserved 6-minute walk distance, at the top of the
9 figure, 2 had among the lowest dystrophin levels,
10 and 2 the highest, as indicated by the arrows.
11 The data are sparse, but there doesn't seem
12 to be much of a correlation between dystrophin
13 levels and change in 6-minute walk test in this
14 particular group of patients.
15 You haven't seen this figure before, but as
16 you recall, patients in study 202 received either
17 30 or 50 milligram per kilogram of eteplirsen for
18 some 3-plus years, so it is worth considering the
19 dose response for the dystrophin detected at
20 week 180. If there were a correlation between the
21 dose of eteplirsen administered and the amount of
22 dystrophin detected, this would help support that

1 eteplirsen produced the dystrophin that was
2 detected.
3 Again, the data are sparse, but there is no
4 support for dose response here. Had a dose
5 response been present, it could have helped support
6 a concept the eteplirsen treatment was in fact
7 responsible for dystrophin detected by Western
8 blot.
9 Now, let's review the clinical evidence. As
10 was discussed by Dr. Farkas, study 201 did not show
11 a significant difference between boys treated with
12 eteplirsen and those treated with placebo for the
13 prespecified primary endpoint.
14 When you think of the 6-minute walk data,
15 it's worth considering just how small the sample
16 size is and about the fragility of the findings.
17 So let's consider the two patients in the low-dose
18 30 milligram per kilo group who quickly lost their
19 ability to ambulate.
20 If by chance they had been randomized to the
21 placebo group, it is likely the trial would have
22 shown a statistically significant difference in

1 favor of the drug, and the result would have been
2 interpreted as showing a large and clinically
3 important treatment effect based on these 12
4 patients.
5 Of course, the study did not turn out that
6 way, but it is important to consider how easily one
7 can be misled by a single study with a small sample
8 size. In addition, just as study 201, study 202
9 did not meet its prespecified clinical endpoint.
10 As you heard this morning, the applicant
11 describes highly statistically significant results
12 in the comparison between boys treated with
13 eteplirsen in study 201/202 and external controls,
14 presenting a difference of 162 meters between the
15 groups.
16 The applicant also describes that in a
17 comparison of eteplirsen to external control over
18 4 years, only 2 of the eteplirsen treated boys lost
19 ambulation compared to 10 of the 13 untreated
20 external controls.
21 The 160 meter difference in the 6-minute
22 walk distance, if demonstrated in an adequate and

1 well-controlled study, would provide evidence of
2 effectiveness, but study 202 was not a randomized
3 controlled trial. And several lines of evidence
4 raise concerns that the differences in ambulation
5 between eteplirsen treated boys and external
6 controls are not related to a treatment effect and
7 may be due to other factors.
8 As was described by Dr. Farkas, there appear
9 to be differences between important baseline
10 characteristics that could affect outcome in boys
11 enrolled in the eteplirsen study compared to those
12 of the registries.
13 For example, the age at initiation of
14 steroid treatment was on average over one year
15 earlier for eteplirsen treated patients. This
16 difference alone could have had a significant
17 impact on clinical outcomes.
18 Dr. Farkas also described evidence
19 suggesting a differential selection of patients for
20 the registry versus for drug studies, which leads
21 to questions about the comparability of the groups.
22 There may also be unrecognized and potentially very

1 important factors, which were not balanced by
2 randomization, between the study and the registry
3 cohorts.
4 There were apparent differences in the
5 administration and on the performance of functional
6 tests between eteplirsen treated boys and those of
7 the registry. You have seen this basic figure in
8 Dr. Farkas' presentation. Patient age is shown on
9 the X-axis and the rise time in the Y-axis.
10 Eteplirsen is shown in red and external control in
11 blue.
12 It is striking that no boy in the Belgium or
13 in the Italian registry had a recorded rise time
14 greater than 22 seconds, whereas some two-thirds of
15 eteplirsen treated boys did. Some rise times were
16 extremely long, in some cases even greater than
17 40 seconds.
18 To be very clear, it wasn't that patients in
19 the registries didn't experience this degree of
20 loss of function, the point is that there is a
21 difference, boys outside of the eteplirsen study do
22 not contribute data for rise time greater than

1 22 seconds. There is a difference, but we cannot
2 really know why there is a difference.
3 Perhaps the eteplirsen boys were more highly
4 motivated, or perhaps they continued to receive
5 encouragement from parents or staff, or perhaps the
6 physician or the physical therapist at the Italian
7 and Belgium sites elected not to perform testing,
8 or to abort testing, once physical function had
9 worsened.
10 Our concern is that there is an apparent
11 difference, and it is precisely these kinds of
12 differences, differences for known or unknown
13 reasons, that can confound comparisons between
14 patients in an open-label drug study and patients
15 in an external observational cohort. And this
16 observation is also supported by the comparison to
17 the CINRG data as presented this morning by
18 Dr. Farkas.
19 Similarly, extreme results were recorded for
20 the 4-step climb time in some eteplirsen treated
21 boys, but again not in registry patients. In
22 addition, as discussed by Dr. Farkas, some boys in

1 the registry had recorded 10-meter run/walk results
2 and at the same time were declared unable to
3 ambulate, which illustrate the subjectivity in the
4 decision to declare a boy as having lost
5 ambulation.
6 These observed differences indicate that the
7 functional test appeared to have subjective
8 elements and that their performance may have been
9 influenced by decisions made by the boys, the
10 caregivers, or by study investigators. These types
11 of differences may have a large impact on test
12 results, and there is no way to correct for that by
13 statistics.
14 Another line of evidence that calls into
15 question interpretation of the 6-minute walk test
16 findings comes from the inconsistencies between
17 6-minute walk test results and other clinical
18 endpoints.
19 As displayed earlier by Dr. Farkas, the left
20 figure shows no clear difference between eteplirsen
21 treated boys and external controls in patterns of
22 changes in rise time by age, with the exception of

1 some more extreme recorded values in eteplirsen
2 treated boys, as we discussed earlier. And the
3 North Star Ambulatory Assessments on the right
4 indicate a similar decline over time for eteplirsen
5 treated patients and external controls, with large
6 overlap in confidence intervals through 4 years of
7 observation.
8 Importantly, there is a substantial overlap
9 of ambulation results between eteplirsen treated
10 boys, external controls, and natural history. As
11 was discussed by Dr. Farkas, on the right, the
12 proportion of eteplirsen treated patients still
13 ambulating at age 14 is not clearly different from
14 what is expected for patients with mutation
15 amenable to exon 51 skipping, as shown by the
16 comparison to the Kaplan-Meier curve of loss of
17 ambulation from the CINRG database on the left.
18 As we heard earlier from Dr. Temple,
19 important issues to consider with external control
20 trials are the possibility of bias before the trial
21 and the possibility of bias during and after the
22 trial. In addition, external control trials are

1 more likely to be persuasive when the effect is
2 very large and when the natural history is highly
3 predictable.
4 We have seen from the CINRG database and the
5 MD STARnet database that the age of loss of
6 ambulation spans over a decade with 25 percent of
7 boys with mutation amenable to exon 51 skipping
8 ambulatory at age 16. That variability is
9 problematic for a historical control study using
10 loss of ambulation or a 6-minute walk test as an
11 endpoint.
12 Overall, the historical control comparison
13 conducted by the applicant raises serious concerns
14 about many factors that should be considered in
15 interpreting a historical control study.
16 As Duchenne muscular dystrophy is an orphan
17 disease, an important issue to consider is whether
18 it would have been possible for the applicant to
19 conduct an adequate and well-controlled study. The
20 answer clearly is yes. This committee discussed in
21 November 2015 an application for another drug
22 developed to treat boys with mutations amenable to

1 exon 51 skipping. As you remember, the application
2 included three placebo-controlled studies, two
3 phase 2 studies with a sample size of about
4 50 patients, and a phase 3 study with over
5 180 patients.
6 In the discussion at the November meeting,
7 the committee raised major concerns about the
8 impact of the sample size of the two phase 2
9 studies on their interpretability. These two phase
10 2 studies, which were randomized and
11 placebo-controlled, dwarf the single eteplirsen
12 study.
13 As we know, the entire eteplirsen efficacy
14 database consists of 12 patients from a single site
15 with a single investigator, with an open-label
16 design, and an external control. While there is no
17 specific minimum number of patients that should be
18 studied to establish effectiveness of a treatment
19 for any rare disease, the number of patients must
20 be sufficient to draw scientific conclusions,
21 taking into account the study design and the study
22 outcome measures.

1 This afternoon, you will discuss whether
2 evidence has been presented to you to support
3 approval based on a biomarker reasonably likely to
4 predict clinical benefit or based on a clinical
5 endpoint.
6 It is important to keep in mind that the
7 difference between accelerated and full approval is
8 the type of endpoint and not the strength of the
9 evidence. As was discussed by Dr. Dunn,
10 substantial evidence is required for both pathways,
11 and accelerated approval cannot be used to
12 compensate for weak or inconsistent clinical
13 findings.
14 Now, I would like to speak directly to the
15 study participants and their families. I want to
16 thank you for your extraordinary commitment and
17 efforts to the incredibly important endeavor to
18 make a new drug available for the treatment of
19 Duchenne muscular dystrophy. I do understand your
20 situation. You have a devastating disease, and you
21 have placed great hope that this experimental
22 treatment will change the course of your disease.

1 I understand your fight because it has been
2 my family's fight. I have a sister who is
3 profoundly disabled since birth, and who almost did
4 not make it through her first days of life. My
5 parents spent considerable time and resources to
6 get her access to experimental treatments.
7 My parents would have done anything,
8 anything to create a brighter future for my sister,
9 and I would do the same for my children. And a
10 number of my close collaborators, some in this
11 room, are facing similar situations.
12 But my role here today as a member of the
13 neurology review division is very different. My
14 role, regardless of the pressure that has been
15 placed on my division, and in particular on the
16 eteplirsen review team, is to present our
17 scientific review and conclusions about eteplirsen.
18 We are a science-based organization. That
19 review has been very careful. Really, it has been
20 exhaustive, and has involved a large
21 multidisciplinary team of reviewers. Even though
22 just a few us are talking to you this morning, I

1 want to assure you that nothing that was presented
2 today represent the unique view of a single
3 reviewer. Instead, it is the product of a large
4 team effort with considerable oversight and
5 feedback by all levels of FDA management.
6 We are looking forward to your testimony
7 this afternoon, and I'm looking forward to a good
8 and productive discussion with the members of the
9 advisory committee. Thank you.
10 **Clarifying Questions**
11 DR. ALEXANDER: Thank you, Dr. Bastings.
12 We now have 15 minutes for questions,
13 clarifying questions for the FDA. Again, please
14 remember to state your name for the record before
15 you speak. And if you can, please direct your
16 questions to a specific presenter.
17 I'll take the prerogative as chair to ask a
18 first question, which is clarifying the selection
19 of the controls from the CINRG study. There was
20 some concern raised on the part of the sponsor, if
21 I understood correctly, regarding the way that the
22 controls were selected and that the individuals

1 that were selected may have represented outliers.
2 So I'm wondering, from the FDA, if someone
3 could speak to how these controls were selected.
4 And in particular, I'm interested in whether there
5 were sensitivity analyses performed using different
6 criteria to select different control groups from
7 the CINRG study, that is, is there an opportunity
8 to look at how the conclusions that one reaches
9 differ based on the control patients selected from
10 CINRG.
11 DR. FARKAS: It's Ron Farkas. Well, let me
12 start. One thing is actually in my mind, it's not
13 exactly clear to me what the issue -- or what the
14 concern was that was raised, but I can describe how
15 we picked the controls. And that was being very
16 careful to separate -- so the review division
17 didn't take a look at any of the data. We took a
18 look at some of the baseline characteristics of the
19 patients without knowing their course, and then
20 matched patients that were similar just on those
21 baseline characteristics, and then the
22 statisticians conducted these comparisons.

1 So there were no -- I mean, on purpose,
2 there were no multiple looks, no sensitivity
3 analyses. It was pick some patients that looked
4 similar. And again, it was not close matching. I
5 think that's something that's important to
6 understand, too. We tried close matching. We
7 actually wrote out a detailed protocol to do close
8 matching, but there weren't any matches, and so we
9 relaxed and relaxed and relaxed until it just
10 seemed like there was kind of some similar baseline
11 characteristics and had the statisticians then do
12 the calculations.
13 DR. ALEXANDER: Thank you. Dr. Ovbiagele?
14 DR. OVBIAGELE: Bruce Ovbiagele. My
15 question is for Dr. Farkas.
16 DR. ALEXANDER: Can you speak into the
17 microphone a little more, please?
18 DR. OVBIAGELE: Sure, sure. My question is
19 for Dr. Farkas. Of course, when you look at the
20 different prognosticators, the big differences you
21 see already with the steroid treatment. And as you
22 might remember from page 39 of the applicant's

1 presentation, the two issues were the age at
2 steroid start, and the other issue was continuous
3 treatment with steroids, which was much, much
4 higher in the eteplirsen group.
5 The applicant looked at the effect of
6 continuous treatment in the external control group
7 and found there was no significant difference. Did
8 you look to see if there was a difference in terms
9 of age at steroid start, in terms of its effect on
10 the outcome?
11 DR. FARKAS: Right. I think that there was
12 a difference in the age at steroid start. But
13 getting back to the daily versus every other day
14 treatment, I think one of the concerns that we have
15 is that it didn't seem like the data was reliable
16 for the daily versus every other day.
17 The NDA came in. We took a look at the
18 counts for daily versus every other day. We raised
19 some concern about that. And then we heard later
20 from the applicant that the data was incorrect as
21 submitted, in that there were more patients on
22 every other day treatment in the historical

1 controls than had been originally reported, which
2 raised some definite concerns in our mind when the
3 data seems to change or wasn't really certain.
4 With regard to seeing if there's a
5 correlation between the treatment given and the
6 clinical course, I think at some point -- I think
7 we tried to be careful to point out that, you know,
8 lack of a correlation between low levels of
9 dystrophin and how patients did on clinical course,
10 it's so very underpowered. And then for some of
11 these other comparisons, we're dividing the
12 patients in half again.
13 So it's true. There wasn't a correlation
14 shown there, but if it's comparing four patients to
15 four other patients, I'm not sure what we can
16 really see.
17 But again, I think that the main point that
18 I tried to make in the original version of the memo
19 that I wrote, and even later on, is that it isn't
20 necessarily large differences that might account
21 for differences in clinical course. I mean, the
22 whole issue that's been identified by experts in

1 DMD is that things that seem small can confound
2 differences between groups.
3 DR. OVBIAGELE: No, I recognize that, but I
4 think the issue of course is that since that of
5 course is one of the issues that has been raised as
6 potentially problematic, at the very least, it
7 might be somewhat reassuring if there was no impact
8 of age of steroid start on the actual clinical
9 outcome in the external control group, if you see
10 what I mean.
11 DR. FARKAS: Yes. I'm just not sure that
12 you can -- so on one particular factor, you can see
13 that very small groups of patients don't divide
14 from each other. But I'm not really sure how much
15 reassurance that gives that the differences
16 couldn't have resulted in a changing clinical
17 course.
18 Of course, but backing up, I mean, in some
19 sense I regret that almost that I brought this
20 up --
21 (Laughter.)
22 DR. FARKAS: -- because the sources of

1 difference between the patients is so large in so
2 many other respects. It was a true point the
3 differences in care can lead to differences in
4 clinical outcome, but it's overshadowed by I think
5 other issues.
6 DR. ALEXANDER: Thank you. Dr. Bastings and
7 then Dr. Hoffman.
8 DR. BASTINGS: Yes, listen. What we know is
9 that patients in the registries started the
10 steroids over one year earlier. The cohort size is
11 just too small to look for any correlation with
12 outcomes, but it's a fact that steroid treatment is
13 effective and widely used in Duchenne muscular
14 dystrophy, and the effect of initiating earlier
15 cannot be overstated.
16 Yes, yes. I'm sorry, I said it backwards.
17 The eteplirsen patients started earlier. Okay.
18 DR. ALEXANDER: Thank you. So the
19 eteplirsen patients started on average one year
20 earlier, started steroids.
21 DR. BASTINGS: Over one year earlier.
22 DR. ALEXANDER: Thank you. Dr. Hoffman?

1 DR. HOFFMAN: Richard Hoffman. I just have
2 a general question. It appears that the FDA is
3 suggesting that another placebo-controlled trial
4 will be needed. And I was wondering if eteplirsen
5 is granted accelerated approval, would a future
6 placebo-controlled trial ever be possible?
7 DR. ALEXANDER: Who is that a question for?
8 DR. HOFFMAN: Anybody in the FDA.
9 DR. ALEXANDER: And when you say possible,
10 are you speaking --
11 DR. HOFFMAN: Well, once it receives
12 accelerated approval, it would be available to all
13 patients, and what patients would want to be a
14 placebo patient at that point?
15 DR. BASTINGS: I think this is a very good
16 question. It seems unlikely that if the drug
17 becomes accessible to patients, that anybody would
18 enroll in a future study that is
19 placebo-controlled.
20 DR. ALEXANDER: Dr. Jenkins?
21 DR. JENKINS: Yes, this is John Jenkins. To
22 help address that question, if you recall the

1 applicant stated their trials are ongoing or
2 planned that they consider to be confirmatory.
3 They had some externally controlled trials for
4 eteplirsen in exon 51 amenable patients. They also
5 had a couple of trials in two other exons that are
6 placebo-controlled hoping that if they can show a
7 significant difference in those placebo-controlled
8 trials in other exons, it would help to validate
9 the findings for eteplirsen.
10 So their confirmatory trials are externally
11 controlled for eteplirsen, placebo-controlled for
12 two other exon-skipping patient populations. But I
13 think you raise a good point about -- anytime a
14 product is approved under accelerated approval, or
15 any type of approval, the question of whether you
16 can then do a trial that's placebo-controlled
17 becomes very challenging, particularly in serious
18 and life-threatening diseases where patients may
19 not be willing to be on placebo.
20 DR. ALEXANDER: Thank you. Dr. Onyike and
21 then Dr. Gordon.
22 DR. ONYIKE: Thank you. Chiadi Onyike.

1 Now, I'd just like to take attention to slide 72,
2 if we could pull that up please. Slide 72. And,
3 yes, acknowledging -- this is for Dr. Farkas.
4 Acknowledging that you've looked at converting
5 multiple levels of evidence and converging
6 outcomes, especially on the clinical side, I just
7 wanted to explore for a minute the subset of
8 subjects in the treatment group who seem to have
9 function -- I mean preserved walking, so the ones
10 that are encircled.
11 I just wondered if you had a way -- I know
12 that most of the comparisons that are done with
13 respect to the two groups are based on a visual
14 analysis, at least the way you presented it, on a
15 visual analysis of the trajectories of the slopes.
16 I just wondered if you had some way to
17 quantitatively analyze the trajectories of those
18 slopes and to compare them. And the reason I say
19 that is because your analysis of any extrapolation
20 as to what might be the future of these subjects
21 was based on other sources of data as opposed to
22 direct comparisons. So I just wondered if you were

1 able to do that.
2 DR. FARKAS: Yes, well I guess the first
3 thing, or to pick up on the last part of what you
4 said, is that everything is external, all the
5 comparisons are external. So this was one group of
6 patients that were selected by the applicant, and
7 other sources of information were basically
8 available at the same time.
9 Part of the issue is -- I mean, the FDA had
10 asked for comparison to multiple sets of data, all
11 the data that might be available. So there is no
12 primary comparison to one historical group versus
13 another historical group.
14 But as to your question of numerical
15 comparisons, I think that's an important point, but
16 that's not the way we can analyze studies like
17 this. This is just the truth about historically
18 controlled trials. There's not really going to be
19 an answer in the numbers because we have to account
20 for these other sources of differences between the
21 groups.
22 So one of the key pieces of advice that we

1 give to people is that if there's the opportunity
2 for doing a historically controlled trial for
3 sponsors, but that unless there's a clear
4 difference, kind of an obvious difference, is the
5 answer in the end between the treated patients and
6 the controls, it wouldn't be possible normally to
7 conclude that it was an effect of the drug and not
8 other differences between the patients and the way
9 the study was conducted.
10 DR. ALEXANDER: I'd like to wait one minute,
11 please, for Dr. Gordon and just go to Dr. Romitti
12 if we can, and then we'll come to Dr. Gordon at the
13 close of this section.
14 DR. ROMITTI: Okay. Paul Romitti. So there
15 has been discussion by both the applicant and the
16 FDA about dialogue that's gone back and forth. And
17 in going through the materials and trying to
18 construct my own timeline of all these dialogues,
19 it's just unclear to me when this recommendation
20 from slide 50 of Dr. Farkas' slides was first
21 given.
22 So that slide, as you see there, says the

1 FDA consistently and strongly encouraged the
2 applicant to perform a randomized double-blind
3 control trial. Can you give us the month and the
4 year that recommendation was first made?
5 DR. FARKAS: Well, I mean I have the month
6 and the year somewhere. It's not right in my head.
7 But I would be able to say that -- so the applicant
8 conducted an analysis at about week 48 in the
9 original study 201 and presented those analyses to
10 us in late 2012 or 2013.
11 We were very much concerned that their
12 analysis was not supportable, not scientifically
13 supportable, and were giving them very strong
14 feedback from that point that we thought that would
15 not be convincing data.
16 DR. ALEXANDER: Dr. Bastings?
17 DR. BASTINGS: I think Dr. Dunn has the
18 exact date. Maybe he does. This has been stated
19 on multiple occasions, not just one time, on
20 multiple occasions. Dr. Dunn?
21 DR. DUNN: I have one exact date for you.
22 Keeping in mind that 1, 2, 3, 4, 5, at least 6

1 people in a row here have said, more times than I
2 can count individually to the sponsor, you need to
3 do that. The date that's in front of me right here
4 from Dr. Breder, the primary reviewer of this
5 application, mentions the importance of conducting
6 a placebo-controlled design using multiple fixed
7 doses in phase 3 development, on June 14th of 2011.
8 DR. ROMITTI: Thank you.
9 DR. ALEXANDER: Thank you.
10 Dr. Cohen [sic], final question for this
11 section? I'm sorry, Dr. Gordon.
12 DR. GORDON: This is Mark Gordon, industry
13 representative. So to follow up on the comments
14 from Dr. Farkas and Dr. Bastings, both of you
15 mentioned that the inability to perform the
16 6-minute walk test was an important determinant in
17 the loss of ambulation.
18 You also mentioned that there was some level
19 or element of a subjective component that possibly
20 influenced the function. So my question is both in
21 the sponsor's study and in CINRG, was there any
22 protocol defined definition of the inability to

1 perform the 6-minute walk test?
2 DR. FARKAS: That's an important point. And
3 the protocols from the natural history study were
4 extremely brief, and they didn't specify anything;
5 extremely brief, just several pages.
6 The protocol for the CINRG study is very
7 detailed. It does make mention of a 25-second
8 cutoff for the 10-meter run/walk, but it doesn't
9 specify very clearly actually how or when endpoints
10 will be measured. And I mean we have, you know
11 Dr. McDonald here, and he's been extremely helpful
12 to the FDA, and we've discussed on the phone with
13 his collaborators.
14 To our understanding, it is a subjective
15 discussion the patients and the parents and the
16 investigators do decide at the study visits what
17 test the patient will attempt and which they won't.
18 DR. ALEXANDER: Thank you. I'd like to give
19 the sponsor a chance to respond either or both to
20 that question and any other very brief responses to
21 questions that have been raised, and then we'll
22 move to the open public hearing.

1 MS. RUFF: Thank you very much. We have
2 Dr. McDonald here, who will answer a question about
3 the choice or the decision about 6-minute walk test
4 and loss in ambulation. And then Dr. Kaye would
5 like to just address a comment about when FDA told
6 us about placebo-controlled studies.
7 DR. MCDONALD: My name is Dr. Craig
8 McDonald. I'm director of neuromuscular disease
9 clinics at University of California Davis. And I'm
10 the study chair of the CINRG Duchenne Natural
11 History study. I've been compensated by Sarepta
12 Therapeutics for my time, and I have no direct
13 financial interest in the outcome of today's
14 meeting.
15 I would like to make some a few very
16 important clarifying points here with regard to the
17 definition of loss of ambulation. If I could have
18 the first slide up.
19 The CINRG has a very specific definition of
20 loss of ambulation. We've published multiple
21 studies in peer reviewed journals based on this
22 definition. It's based on a physician assessment,

1 patient and parent report a full-time wheelchair
2 use on a standard CRF, so there's no independent
3 household ambulation or minimal ambulation.
4 This is, when available, corroborated by the
5 loss of the ability to perform the 10-meter
6 walk/run test. That's a very different definition
7 and standard than what I think the sponsor
8 appropriately used in this trial. If I could have
9 the next slide up.
10 The sponsor defines the loss of ambulation
11 as the acquisition of a 6-minute walk distance of
12 zero. And what you see on the left is actually the
13 worldwide available literature on 6-minute walk
14 distance that has been obtained both in placebo
15 arms as well as registries.
16 The data on the right is actually published
17 registry information from Goemans. What's really
18 quite dramatic here is you see that the data is
19 almost superimposable in terms of that obtained by
20 natural history studies and that obtained in
21 placebo-controlled arms of studies.
22 So this really I think addresses the concern

1 about motivational aspects or biases, where we're
2 seeing very similar data. The most important point
3 here is if you look at this definition of loss of
4 ambulation, virtually only about 2 to 3 percent of
5 patients, based on a 6-minute walk distance
6 definition, continue ambulating past the age of 15.
7 If I could have the next slide. This was
8 the CINRG data that was discussed by the sponsor as
9 well as by Dr. Farkas. And what we see here is the
10 patients from the CINRG cohort exon 51 mutations,
11 the 25 percent of patients that Dr. Farkas alluded
12 to there, that's based on a CINRG definition of
13 inability to perform the 6-minute walk test as well
14 as physician and patient determination of full-time
15 wheelchair use.
16 I should point out that this is rather
17 limited data set. It only represents 3 patients,
18 that when you talk about 25 percent, that only
19 represents 3 patients. And what we see in the blue
20 line there is something very different I think with
21 the eteplirsen treated patients. We're seeing,
22 first of all, those patients haven't reached the

1 age of 16 yet. But what we see is 10 of
2 12 patients still walking based on rigorous
3 definition of 6-minute walk distance as the
4 definition.
5 If I could just finish by focusing on rise
6 time, as this has been something that has been an
7 important point made by the FDA. If I could have
8 the next slide up.
9 So rise time and rise ability is really an
10 important prognostic endpoint. If I could have the
11 next slide up. And I think it's important to point
12 out here, there's a matter of definitions. The FDA
13 focuses on the absolute time taken to perform the
14 test. The sponsor, on the other hand, really
15 focuses on the critical importance of the loss of
16 this endpoint in terms of independent ability to
17 perform the test.
18 So the loss of this endpoint as we know it
19 is really what's prognostic. And this is CINRG
20 data here. If we could pull up the slide actually
21 on this screen. Slide up, please.
22 This is actually CINRG data on rise ability

1 and loss of rise ability and its prognostic
2 importance for loss of ability to ambulate. And
3 what you see here actually in the CINRG data is
4 it's not the absolute value of rise time that's of
5 prognostic value, it's the loss of the rise
6 ability.
7 So what you see there in the red are those
8 patients who have completely lost the ability to
9 rise independently. And virtually 50 percent of
10 those patients have lost the ability to ambulate
11 within 12 months. And in fact, 70 percent of those
12 patients lose the ability to ambulate at 24 months.
13 If you look at purple and blue lines at the
14 top, that shows the survival curves when rise time
15 is less than 5 seconds, 5 to 10 seconds, or greater
16 than 10 seconds. The actual rise time is not a
17 prognostic value. The importance is the loss of
18 rise ability independently.
19 If we could just show the next slide, this
20 shows how the sponsor has actually focused on loss
21 of rise ability independently. And what you see
22 there is 3 years out a high percentage of

1 eteplirsen treated patients have maintained the
2 rise ability, a very small percentage of the
3 external controls. But I think what's even more
4 striking is when you look at years 1, 2 and 3, the
5 patients that have lost rise ability have still
6 maintained the ability to ambulate over a prolonged
7 period of time. Thank you.
8 DR. ALEXANDER: Thank you very much. I do
9 want to move on to the portion of the open public
10 hearing.
11 (Applause.)
12 DR. ALEXANDER: Thank you very much.
13 Dr. Bastings, and then we'll move on to the
14 open public hearing.
15 DR. BASTINGS: I would like the applicant to
16 bring back the slide comparing the Kaplan-Meier
17 curve from the eteplirsen patients to the CINRG
18 database that they just showed.
19 DR. ALEXANDER: Can the sponsor please
20 project that slide?
21 DR. BASTINGS: Yes. I would like to point
22 out that that slide is totally misleading, because

1 most of the eteplirsen patients shown in blue here
2 have not reached the age 15. So there is just no
3 way to make that sort of comparison because they
4 simply have not reached that age yet.
5 **Open Public Hearing**
6 DR. ALEXANDER: Thank you. We will have
7 more time for discussion during the question period
8 after the open public hearing.
9 Both the Food and Drug Administration and
10 the public believe in a transparent process for
11 information-gathering and decision-making. To
12 ensure such transparency at the open public hearing
13 session of the advisory committee meeting, FDA
14 believes that it is important to understand the
15 context of an individual's presentation.
16 For this reason, FDA encourages you, the
17 open public hearing speaker, at the beginning of
18 your written or oral statement, to advise the
19 committee of any financial relationship that you
20 have with the sponsor, its product, and if known,
21 its direct competitors.
22 For example, this financial information may

1 include the sponsor's payment of your travel,
2 lodging, or other expenses in connection with your
3 attendance at the meeting. Likewise, FDA
4 encourages you at the beginning of your statement
5 to advise the committee if you do not have such
6 financial relationships.
7 If you choose not to address this issue of
8 financial relationships at the beginning of your
9 statement, it will not preclude you from speaking.
10 The FDA and this committee place great
11 importance on the open public hearing process. The
12 insights and comment provided can help the agency
13 and this committee in their consideration of the
14 issues before them.
15 That said, in many instances and for many
16 topics, there will be a variety of opinions. One
17 of our goals today is for this open public hearing
18 to be concluded in a fair and open way where every
19 participant is listened to carefully and treated
20 with dignity, courtesy, and respect. Therefore,
21 please speak only when recognized by the
22 chairperson. Thank you for your cooperation.

1 Will speaker number 1 please come to the
2 podium and introduce yourself? Please state your
3 name and any organization you are representing for
4 the record.
5 MR. FITZPATRICK: Good afternoon, and thank
6 you for allowing me --
7 DR. ALEXANDER: Can you please speak a
8 little more directly into the microphone?
9 Microphone on, please. We need audio at the
10 podium.
11 MR. FITZPATRICK: Good afternoon, and thank
12 you for the opportunity to address the advisory
13 panel this afternoon. My name is Mike Fitzpatrick.
14 I represent the 8th Congressional District of
15 Pennsylvania.
16 I want to begin by thanking you for holding
17 this hearing, as well as for the agency's ongoing
18 commitment to use its full range of tools and
19 authorities to expeditiously review candidate
20 therapies for rare but devastating diseases, like
21 Duchenne muscular dystrophy.
22 I'm a member of the Congressional Rare

1 Disease Caucus, and I've discussed and advocated
2 for funding and research opportunities for a number
3 of medical conditions, many of which have
4 connections to my district in Bucks County,
5 Pennsylvania.
6 That connection for Duchenne muscular
7 dystrophy is 15-year-old Jake Wesley, who suffers
8 from this terrible disease. Sadly, like so many in
9 Jake's position, the decline of his health has been
10 precipitous. The risk of doing nothing for someone
11 like Jake is unacceptable. I've seen his disease
12 progress year after year, robbing him along the way
13 of any sense of his own independence, and Jake
14 deserves better.
15 There is a path forward, one which could
16 alter the lives of all Duchenne patients in a very
17 positive way, giving them a chance to live a
18 longer, better life. As you know, in recent years
19 the Congress along with the FDA have made
20 tremendous progress toward, through the Food and
21 Drug Administration Safety and Innovation Act,
22 providing new therapies intended to treat persons

1 with life-threatening and severely debilitating
2 illnesses, especially where no satisfactory
3 alternative therapy exists, in this case Duchenne.
4 The accelerated approval pathway outlined in
5 Section 901 of the Act, allows demonstrably safe
6 therapies that treat an unmet medical need, and
7 appear to be efficacious, even with some
8 uncertainty, to avoid the years of regulatory
9 barriers and become accessible earlier to patients
10 who otherwise have no other option.
11 FDA has been most successful at applying
12 flexibility in oncology and HIV/AIDS to speed
13 patient access to apparently safe treatments, but
14 the need and the opportunity to adopt innovative
15 and flexible approaches to the review of rare
16 disease drugs has never been greater than it is
17 today. Children like Jake are waiting.
18 That is why today my urgent call is echoed
19 by 108 other bipartisan members of Congress who
20 have joined me in writing to Dr. Janet Woodcock,
21 and I would ask, with the panel's permission, that
22 this letter, signed by 108 of my colleagues, be

1 entered as a part of this record today.
2 I remain committed to ensuring --
3 (Applause.)
4 MR. FITZPATRICK: -- and it's difficult to
5 get 108 of my colleagues to agree -- [mic off].
6 DR. ALEXANDER: Thank you very much.
7 (Applause.)
8 Will speaker number 2 please come to the
9 podium and introduce yourself. Please state your
10 name and any organization you are representing for
11 the record.
12 MS. JURACK: Yes. Good afternoon,
13 committee. My name is Karen Jurack, and I have not
14 been financially compensated by anyone to be here
15 today. I am the mother of a soon to be
16 15-year-old. His name is Joshua. He has been
17 battling Duchenne muscular dystrophy for 10 years
18 now. He was diagnosed at 4 and a half with a
19 deletion mutation in genes 49 and 50, making him a
20 perfect candidate for exon 51 skipping therapies.
21 Joshua lost his ability to walk at age 9,
22 had spinal fusion surgery at age 13, and since the

1 surgery Joshua has lost a great deal of his arm
2 mobility. He can no longer feed himself, which is
3 a distressing loss of independence.
4 As a parent, it's very difficult to watch
5 your child continue to get weaker every day. You
6 feel absolutely helpless, and you never believe
7 you're doing enough to help your child get better.
8 Because steroids alone are not sufficient, I
9 constantly check the availability of clinical
10 trials for Joshua. And unfortunately, in the
11 majority of cases, he did not qualify for those
12 studies because he has not been ambulatory for
13 several years.
14 When I found the Sarepta eteplirsen study, I
15 was delighted because the study parameters were
16 such that we could potentially qualify. In March
17 2015, Joshua and I went to Johns Hopkins and tried
18 to take part in this trial, however he was excluded
19 because he could not lift a glass of water to his
20 mouth. We were devastated by this news.
21 In the fall of 2015, as part of their
22 medical training, Joshua was interviewed by some

1 medical students. One of the questions he was
2 asked was what he worries most about for the
3 future. I fully expected him to say college, but
4 very calmly and soberly said he was worried most
5 about his lungs and heart failing him. This shows
6 the reality in which he lives, the thoughts of his
7 mortality that totally consume his every being.
8 Joshua has a brilliant mind, however he is
9 trapped in a body that doesn't work. He's always
10 been an exceptional child. He's an overachiever in
11 academics, scouting life, and unfortunately with
12 Duchenne. Joshua's muscular dystrophy seems to be
13 progressing at a faster rate than most of his
14 peers. Now more than ever time is of the essence
15 for our family.
16 Despite his physical decline, Joshua remains
17 optimistic and determined to meet his goals in
18 life. For example, he'll be completing his Eagle
19 Scout service project this coming Saturday.
20 Although Joshua was not included in the
21 trial for eteplirsen, we would welcome the
22 opportunity to have access to this drug therapy.

1 For Joshua, success would include gaining some
2 strength in his arms where he could once again feed
3 himself and not be secluded from others during
4 school lunch. If there's the slightest chance exon
5 skipping could improve and prolong his quality of
6 life, we would be thrilled with the prospect.
7 Exon skipping therapies offer our family and
8 many like ours a tangible hope that a viable option
9 for slowing the progression of Duchenne is at hand.
10 With exon 51 skipping therapies, Joshua's future
11 may become more of a reality. Thank you for your
12 time.
13 (Applause.)
14 DR. ALEXANDER: Thank you very much. Will
15 speaker number 3 please come to the podium and
16 introduce yourself. Please state your name and any
17 organization you are representing for the record.
18 MR. BASILE: My name is Carlo Basile, and
19 Make Duchenne History Coalition paid for my trip
20 today to be here. I thank you for the opportunity
21 to speak today. Again, my name is Carlo Basile.
22 I'm chief secretary to Massachusetts Governor

1 Baker. He wants everyone in the Duchenne family to
2 know he stands behind us.
3 As one public servant to another, I want to
4 remind you that your job's here to serve the
5 people. But before that, before I go on -- and
6 everything I say is as a parent and not as the
7 governor's chief secretary -- I find it insulting
8 that someone would tell me or these people behind
9 me that you understand. Unless you have a child
10 that has muscular dystrophy, you don't understand.
11 Today, your job is to serve all Americans
12 who are living with Duchenne, have lost one to
13 Duchenne, or yet to be diagnosed or born with
14 Duchenne. To help inform your deliberations, I
15 would like to make two important points lacking in
16 the FDA's framing of the vote questions. These
17 points are important to ensuring you should uphold
18 the integrity of the vote process.
19 First, the FDA states in framing the vote
20 questions that, quote, "The intent of the statutory
21 requirements is to reduce the chance of incorrect
22 conclusion that a drug is effective when in fact it

1 is not effective."
2 Earlier today, Christine McSherry mentioned
3 this is type 1 error. I'm disappointed that there
4 is no similar mention in FDA's briefing materials
5 about type 2 errors, where the FDA fails or delays
6 approval of a drug that is in fact effective. I
7 would like the FDA to address after the open public
8 hearing how they are accounting for type 2 errors
9 today.
10 Every day with my son, I witness the human
11 costs would be making type 2 error Duchenne in the
12 Duchenne population. In the past year alone,
13 Carlo Jr. has followed the natural history of
14 Duchenne and lost the ability to carry his
15 backpack, run with his brother at a natural speed,
16 bouncing a basketball, amongst other things. And
17 the next three years, I don't even want to imagine
18 what he'll be facing.
19 My second point is, the FDA emphasizes
20 upholding statutory standards of approval. Yes, a
21 drug must demonstrate effectiveness to be approved.
22 But according to the regulations, the FDA also must

1 apply the broadest flexibility in applying the
2 statutory standards for the drugs that treat
3 life-threatening, severely debilitating diseases,
4 especially where no alternative therapy exists.
5 Just the context, the Congress passed the
6 FDASIA 2 -- [mic off].
7 DR. ALEXANDER: Thank you very much for your
8 comments.
9 (Applause.)
10 DR. ALEXANDER: And I'd like to ask if
11 everyone would mind holding their applause until
12 the end. We have about 52 speakers that we'll be
13 hearing from and would just request that you hold
14 your applause until the final speaker. The next
15 speaker is speaker number 4. If you could please
16 come to the podium and state your name and any
17 organization that you're representing for the
18 record.
19 MS. MINER: My name is Malanie Miner. My
20 travel was paid for by Make Duchenne History
21 Coalition. My 17-year-old son, Cobi, has Duchenne.
22 By the time Cobi was 3 years old, we had a feeling

1 something just wasn't quite right. By the time he
2 was 5, we got a diagnosis of Duchenne.
3 During a visit to Cincinnati Children's
4 Hospital in 2011, we were told that Cobi could be a
5 candidate for a new drug trial, the same trial that
6 is under review today. An initial pre-screening
7 showed that he met all of the strict requirements
8 for this trial. At this time, Cobi was ambulatory
9 and relatively healthy for an 11-year-old with
10 Duchenne.
11 Unfortunately, there was a delay in the
12 start of the trial, and by the time Cobi was
13 screened in July of 2011, at age 11, his baseline
14 walk test had declined so much that he no longer
15 met the study's strict trial criteria. We were
16 devastated by the decline at only 11 years old.
17 Cobi broke his leg soon after and never
18 walked again. It is very bittersweet for me to be
19 here and see the boys who have been on eteplirsen
20 since 2011 and compare them to my son. Five years
21 ago, Cobi was just like them, but now the
22 difference is stark and painful.

1 A few weeks ago, Cobi contracted pneumonia.
2 He suffered from septic shock. During a prolonged
3 stay in the ICU, we heard more devastating news.
4 Cobi is now in heart failure.
5 In their briefing documents, FDA states that
6 the loss of ambulation ranges from 8 to 18 years
7 old. This is not what I see in the hundreds of
8 people I know in the Duchenne community. There are
9 a lot of 9 and 10-year-olds with Duchenne dying,
10 yet there was no mention of that in the briefing
11 documents.
12 There are a lot more boys like Cobi who have
13 Duchenne dying in their late teens than there are
14 ones walking until their late teens, as described
15 in the FDA's briefing documents. My son is the
16 true placebo and a true natural history of
17 Duchenne, the eteplirsen boys are not.
18 In summary, Cobi would be with us today, but
19 because of his heart failure he could not attend.
20 And if eteplirsen is approved, I believe that it
21 could still help Cobi. If he had access to it, it
22 could still potentially improve and prolong his

1 life.

2 (Applause.)

3 DR. ALEXANDER: Thank you for sharing your

4 experience. Will speaker number 5 please come to

5 the podium and introduce yourself? Please state

6 your name and any organization you are representing

7 for the record.

8 MS. McSHERRY: Thank you, Malanie.

9 This is Christine McSherry. Jett Foundation

10 and Make Duchenne History Coalition provided the

11 funds for my travel this morning. Just to get to

12 Dr. Bastings point, I just want to remind FDA and

13 the panel that one of the reasons why the parents

14 came to you before the data was presented is

15 because we saw those signs that the drug was

16 working, and therefore a placebo-controlled trial

17 would be not feasible. I just wanted to make the

18 comment.

19 But I'd like to talk to you today as mother

20 and advocate. You did hear from me this morning in

21 the Patient Reported Outcome project. My son Jett

22 was diagnosed when he was 5, today he's 20. Jett

1 took his last steps at the age of 13 despite being
2 on 40 milligrams of daily deflazacort. It's a high
3 dose. Last year, Jett enrolled in a limited
4 ambulation safety study for eteplirsen, and in my
5 view, he has stabilized and some things have gotten
6 better, and you've heard about those things.
7 But that's not what I'm here to talk to you
8 about today. I want to make sure that the panel
9 understands what all of us are advocating for.
10 We're asking the FDA to approve a drug that's
11 demonstrated consistently efficacy on multiple
12 measures.
13 We're asking that the agency utilize
14 flexibility in the tools it has to approve a
15 remarkably safe drug while pursuing confirmatory
16 trials. If as a result of those trials, it becomes
17 clear that eteplirsen is not working, we will stand
18 behind the agency should it decide to remove it
19 from the market. You see, we only want drugs that
20 work.
21 We're not asking the FDA to lower its
22 standards or grant wishes to a desperate community.

1 We are a community that is well-informed, a
2 community that funds and drives research, a
3 community that writes draft guidance for drug
4 development. We are here in large numbers because
5 eteplirsen has met the safety and effectiveness
6 standards for accelerated approval.
7 As a mother and an advocate, I'm surprised
8 and disappointed by the briefing documents released
9 in January, even more so by those released last
10 week. What's clear from those documents is that
11 the Division of Neurology is seeking to send a
12 message to Sarepta, industry, and the rare disease
13 community; a message that we will only accept a
14 large randomized, double-blind, placebo-controlled
15 trial, no matter what the severity or the disease.
16 We were very encouraged when FDA issued the
17 DMD draft guidance, which included historically
18 controlled data as a potential pathway for
19 approval. Now to see the FDA distancing itself so
20 aggressively from that guidance is extremely
21 disheartening.
22 If FDA really wanted a large placebo-

1 controlled trial, why did the neurology division
2 guide the company to start a single-arm study in
3 the 4 to 6-year-olds who would age into that study?
4 There's virtually no one left who is drug naïve to
5 enter into such a trial. We expect the FDA to
6 provide clear, viable regulatory pathways towards
7 approval. The goal post cannot be changed.
8 Twenty-five years ago, FDA utilized
9 accelerated approval to save a generation of young
10 men dying of AIDS. Today the agency has another
11 generation of young men that they could also save
12 from Duchenne. It's time for the neurology
13 division to join oncology and the anti-viral
14 divisions, among others, follow [mic off].
15 (Applause.)
16 DR. ALEXANDER: Thank you. Will speaker
17 number 6 please come to the podium and introduce
18 yourself? Please state your name and any
19 organization you are representing for the record.
20 MR. WILLIAMS: My name is Brady Williams.
21 My friend, Bryson Foster, a former NBA goodwill
22 ambassador, said if we can find a cure, we can save

1 people's lives. We have not found a cure, but we
2 are saving lives with this drug. The average boy
3 stops walking with DMD around 10 years old, but I
4 am still going strong, nearly 15 years old.
5 MS. WILLIAMS: My name is Martha Williams,
6 and the Make Duchenne History Coalition arranged
7 for our travel. This is my son Brady standing here
8 with me today. He walked in at 14 years and
9 11 months old. He's still able to walk
10 independently, other than long distances, and
11 that's quite an accomplishment for any boy Brady's
12 age with Duchenne muscular dystrophy.
13 Brady's steroid usage has only changed once
14 in the 9 and a half years that he's been on it.
15 The change was simply due to the recommended dosage
16 for his weight, and he's still under-dosed for his
17 weight. He's been off and on physical therapy with
18 many extended breaks.
19 The therapy consists of 1 to 2 times a week,
20 in the pool and on land, and there's been times
21 that we've had a break or more from therapy. At
22 home we do some stretches, and he wears night

1 splints a few nights a week, but this is the
2 typical regimen for a boy with DMD, and this is by
3 no means to be considered an intense treatment.
4 Although Brady still falls on occasion,
5 these falls have gone from almost a daily
6 occurrence to 1 to 2 times a month. It's a relief
7 to know that we don't have to fear a fall every
8 time he's out of our sight. At MDA camp, Brady is
9 one of the only boys in his age range with Duchenne
10 muscular dystrophy still able to walk.
11 He can get out of the pool and jump in from
12 the side independently. He can keep his head above
13 water for 10 minutes at a time, and before he was
14 on the medication, he would sink immediately below
15 the water because he didn't have enough strength in
16 his neck to hold himself up.
17 Brady's lung function continues to be good,
18 and his heart is functioning normally, which was
19 confirmed with his recent cardiac MRI. Although
20 Brady's ability to walk is reassuring us that this
21 treatment is working as intended, him having good
22 lung and heart function is more than we could hope

1 for at his age with this disease.
2 Brady has been infused weekly for 5 and a
3 half years without missing one single dose. Other
4 than the occasional bruise, which would be expected
5 with any needle, he has had zero side effects from
6 this medication.
7 We have no doubt without the treatment,
8 Brady would have been confined to a wheelchair full
9 time, and we would not see the heart and lung
10 function he has from being in this trial. This
11 medication is safe, it's effective, it's working.
12 Brady along with these other boys have
13 endured more than most do in a lifetime. The
14 approval of this medicine is essential to ensure
15 his continued stabilization for his heart and lungs
16 and reduce the overall decline for him and the
17 others afflicted with Duchenne muscular dystrophy.
18 Thank you.
19 (Applause.)
20 DR. ALEXANDER: Thank you very much. Once
21 again, please hold your applause until the final
22 speaker has spoken.

1 Will speakers number 7 please come to the
2 podium and introduce yourselves? Please state your
3 names and any organization you're representing for
4 the record.
5 MR. DUNNE: My name is Chris Dunne. My wife
6 and I are the parents of Ryan, a 12-year-old boy
7 who was born with Duchenne muscular dystrophy.
8 Being a parent of a child with DMD means that there
9 are a lot of milestones ahead. In the not too
10 distant future, Ryan will lose the ability to walk
11 and will be forced to rely on a wheelchair.
12 After that, Ryan will lose the ability to go
13 to the bathroom on his own, and then he will not be
14 able to feed himself. Finally, he will lose the
15 ability to breathe on his own, and he will die
16 before he has a chance to truly live.
17 Those are just a few challenges that Ryan
18 has to look forward to. He already has to live
19 with the fact that he cannot play with his peers,
20 that he has to struggle in school, that as a fifth
21 grader he is smaller than most second graders
22 because he has to take steroids all of his life.

1 In 2014, Ryan had the opportunity to become
2 part of the eteplirsen trial. We jumped at the
3 chance. Ryan did not jump because he had lost the
4 ability when he was 9. Ryan's been receiving
5 eteplirsen for 72 weeks without any adverse events
6 or side effects. Time has always been the worst
7 enemy of children with DMD. Eteplirsen has however
8 given us a reason to hope.
9 The people who see Ryan daily, teachers,
10 therapists, friends and family, notice that things
11 are better, less falls, more stamina, greater
12 strength, and even a regained ability to jump. All
13 this on a steroid dosage that is less than half of
14 the standard 0.9 milligrams per kilogram.
15 Not a single person here believes that
16 eteplirsen is the cure for DMD, but no one can deny
17 that it is a valuable treatment. Eteplirsen is as
18 important to boys with DMD as insulin is for
19 diabetics. We know what will happen if our
20 children are denied this life-saving medicine, a
21 steady downward progression ending in an untimely
22 death. You can change that today.

1 (Applause.)

2 MR. PASCHAL: Hello. My name is Kris

3 Paschal, and I am a father of a 13-year-old boy,

4 Samuel, with Duchenne muscular dystrophy. Our son

5 Sam and our family moved to England in 2011 because

6 we didn't have much faith in the FDA's ability to

7 take up orphan drugs, and thought the best

8 opportunity would be in Europe where Sam

9 participated in the drisapersen trial. We have

10 since repatriated and become a part of the

11 eteplirsen trial.

12 The difference between the two have and

13 night and day in efficacy. Sam had no less than

14 6 times when the protein in his urine on the other

15 drug was elevated. He has never had that since

16 we've been on eteplirsen, so the efficacy is night

17 and day.

18 I'd like to remark that this morning, we

19 spoke of the law behind this, and I think Estes

20 Kefauver and Oren Harris would be appalled at the

21 process we are going through. It was meant to

22 protect the consumer who was uneducated from the

1 unscrupulous drug companies. I think today we have
2 clear evidence that we have an educated consumer
3 here who is asking that you seriously consider this
4 given the merits of the drug.
5 (Applause.)
6 DR. ALEXANDER: Thank you very much. Will
7 speaker number 8 please come to the podium and
8 introduce yourself? Please state your name and any
9 organization you are representing for the record.
10 DR. FLETCHER: My name is Sue Fletcher. I'm
11 a researcher with Murdoch University in Australia.
12 We pioneered PMOs for exon skipping and developed
13 the eteplirsen sequence license to Sarepta, I
14 therefore have a financial interest in the outcomes
15 of today. I am also a consultant to Sarepta.
16 In this presentation, I comment on three
17 issues: the validity of Western blot to assess
18 dystrophin expression, how much dystrophin is
19 normal, and lessons learned from the mdx mouse.
20 Western blotting is a useful technique for
21 assessing protein quantity and quality and
22 comparing between samples within a study.

1 At this time, no universal dystrophin
2 reference standard is available, and therefore,
3 each study must stand alone and be accompanied by
4 valid reference standards. This means that we
5 cannot equate dystrophin expression in one study
6 with data from another that uses a difference
7 reference and different protocols.
8 Dystrophin levels cited in Duchenne and
9 Becker are mostly from early reports relying on
10 technologies not consistent with accurate
11 quantitation. If signals from the test and
12 reference samples do not all lie within the linear
13 range, quantitation is not possible.
14 A black image band from a blot means pixels
15 are saturated, and therefore using current
16 technology are interpreted as infinity. I present
17 a blot showing muscle protein expression in
18 non-dystrophin subjects; dystrophin in samples D
19 and E differ by approximately 9-fold. It is
20 obvious that such a broad range in dystrophin
21 levels would have implications for the analysis of
22 de novo dystrophin expression in samples.

1 The dystrophin Western blot data presented
2 by Sarepta demonstrates greater scientific rigor
3 than is evident in any other published reports I
4 have studied. Dystrophin expression in untreated
5 DMD muscle is reported as average 0.08 percent
6 relative to the reference sample used, and that in
7 muscle from treated patients 11-fold higher.
8 Use of a different reference sample and/or
9 protocol would deliver different numbers, but it is
10 the increase in dystrophin expression after
11 eteplirsen treatment that is the important outcome.
12 If the 180-week dystrophin analysis of 0.9 was
13 relative to the higher dystrophin on our
14 immunoblot, that is sample E, then comparison to
15 sample E would yield a figure of 8.1 percent. I
16 use this data to illustrate it is not the actual
17 number that is important, it is the increase in
18 dystrophin after treatment.
19 My extensive experience as a scientist
20 working on mdx mice has yielded key findings
21 relevant to the discussion today. Systemic PMO 23
22 treatment in mdx mouse induces de novo dystrophin

1 in all muscles, which correlates with improved
2 function. PMO M23 [ph] treatment initiated in
3 newborn mice prevents the onset of dystrophin
4 pathology.
5 In closing, based on all our research and
6 the data presented by Sarepta, it is evident that
7 eteplirsen induces de novo dystrophin expression.
8 I believe that it is reasonable to conclude that
9 the increase in dystrophin is responsible for the
10 clinical benefit reported in the patients. Thank
11 you.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker number 9 please come to the podium and
15 introduce yourself? Please state your name and any
16 organization you are representing for the record.
17 DR. BYRNE: Mr. Chairman and the committee,
18 my name is Barry Byrne. I'm a clinician scientist
19 with experience caring for boys with Duchenne
20 muscular dystrophy as a pediatric cardiologist.
21 I'm a member of the FDA committee on
22 cellular tissue and gene therapies advising CBER,

1 and I have no financial interest in the outcome of
2 this meeting. I've served as a scientific advisor
3 to Sarepta, and our center is a hub site for the
4 PROMOVI phase 3 study. Most importantly for the
5 discussion today, I am privileged to care for one
6 of the patients in the 201/202 study who is here to
7 share their experience as a participant of the
8 pivotal eteplirsen study under review.
9 My objective in these brief comments is to
10 draw a parallel between the study of eteplirsen and
11 a related pivotal study leading to the marketing
12 approval of Myozyme for Pompe disease. Our center
13 was the lead enrolling site of the Myozyme studies,
14 and I think a comparison to this small study using
15 historical cohort is relevant to the discussion
16 today.
17 The primary endpoint of the Myozyme study
18 was ventilator-free survival. The secondary
19 endpoint of overall survival was compared to an
20 only 2 percent survival rate in the historical
21 cohort. Based on the comparison to this historical
22 cohort, Myozyme was approved for commercial use

1 when the initial findings showed overall improved
2 survival. After 4 years of treatment, 44 percent,
3 or 7 of the 16 subjects were alive without assisted
4 inhalation.
5 In comparison, the clinical endpoint of
6 functional ambulation is an equally critical
7 important endpoint in Duchenne. The importance of
8 this type of binary endpoint is often emphasized by
9 the agency and experts in the field. I think that
10 the finding of 83 percent of eteplirsen study
11 participants who are ambulant after 4 years to
12 therapy compared to the finding of 44 percent
13 survival in the Myozyme study should not be
14 overlooked.
15 Movement and freedom of ambulation is really
16 life sustaining for a boy with Duchenne, and the
17 open-label Pompe studies relied on historical
18 cohorts since we accept that pediatric studies
19 require a prospect for direct benefit, therefore
20 prohibiting a contemporary placebo control.
21 So I think Sarepta has designed and
22 conducted the 201/202 studies with these important

1 principles in mind, and they've been diligent as a
2 sponsor of the studies under consideration today.
3 Although this is a small study, the effect is in
4 fact well controlled given the constraints of
5 pediatric rare disease research. And based on
6 these observations of my patient in the study and
7 in the light of the findings today, I strongly
8 believe eteplirsen meets the standard for
9 substantial evidence of effectiveness and warrants
10 approval in boys with Duchenne muscular dystrophy.
11 Thank you.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker number 10 please come to the podium and
15 introduce yourself? Please state your name and any
16 organization you are representing for the record.
17 DR. GOTTSCHALK: Hi, I'm Dr. Laura
18 Gottschalk speaking on behalf of the National
19 Center for Health Research. I received my PhD from
20 Johns Hopkins School of Medicine. Our center
21 scrutinizes medical data and provides objective
22 health information to patients and providers. We

1 do not accept funding from pharmaceutical
2 companies, and I have no conflicts of interest.
3 We agree that FDA should get safe and
4 effective new treatments to patients as quickly as
5 possible, especially for devastating disease such
6 as Duchenne. We were hoping for persuasive data on
7 eteplirsen, but with only 12 patients, inadequate
8 control groups, and variation in disease
9 progression, approval would only be appropriate if
10 there is very clear benefit. Sarepta was warned
11 about this in advance.
12 Unfortunately, the data do not meet a
13 scientific standard of evidence of effectiveness.
14 While there was an increase in dystrophin, the
15 Western blot shows a total amount of protein below
16 what is estimated to be clinically significant, and
17 a 6-minute walk test was fraught with problems.
18 After less than half a year, Sarepta eliminated
19 placebo controls for a drug intended for lifelong
20 use. It became an open-label study, which could
21 influence the walk test results.
22 There are problems with the historical

1 controls used such as evidence that boys in the
2 control group had little incentive to comply with
3 the walk test, and so some were mislabeled as
4 non-ambulatory. Two of the patients did very
5 poorly on the drug. Sarepta assumes that their
6 early loss of ambulation was related to treatment,
7 but this hasn't been proven. Any one of these
8 problems undermines the study results, but to have
9 all these problems and others is simply
10 unacceptable.
11 U.S. law requires evidence of safety and
12 effectiveness. The burden of proof lies with
13 Sarepta. If this drug actually works, then Sarepta
14 has failed itself, the patient, and their families
15 by not conducting a better study that could provide
16 convincing evidence showing it works.
17 Since 2014, Sarepta has been enrolling
18 patients into a larger study, more than 100 boys,
19 but none of those results were provided to the FDA
20 for this meeting. Why not? Even 40 more patients
21 would provide better evidence and the results show
22 clear benefits.

1 Sarepta should have provided the additional
2 data to FDA to examine and provide to this advisory
3 committee. That's how the process works. This
4 committee should not make a decision based on
5 evidence that has not been vetted by the FDA.
6 You're hearing from many patients and family
7 members today who believe in this drug. Your role
8 on the advisory committee is to pressure the
9 company to provide scientific evidence before
10 approval, not to pressure the FDA to ignore the
11 lack of scientific evidence.
12 Your decision today will send a message
13 about whether scientific standards should matter to
14 the FDA. I am very sorry to say that approval of
15 eteplirsen based on today's data would set a
16 dangerously low bar for drugs in the future.
17 We all want an effective drug for Duchenne.
18 I strongly urge the FDA and Sarepta to work
19 together as quickly as possible to prove whether or
20 not eteplirsen is that drug.
21 Treatments for rare diseases can be proven
22 on small samples but not based on 12 patients in a

1 poorly designed study with ambiguous results.
2 Thanks.
3 DR. ALEXANDER: Thank you. Will speaker
4 number 11 please come to the podium and introduce
5 yourself? Please state your name and any
6 organization you are representing for the record.
7 DR. LOWES: I would like to disclose that my
8 trip was paid for by the Make Duchenne History
9 consortium, and I am involved in the ongoing
10 Sarepta trials. My name is Linda Lowes, and I am
11 the lead therapist on the eteplirsen trial, which
12 means that along with Lindsay Alfano, I collected
13 all of the trial outcome measures.
14 I have been a physical therapist for over
15 20 years, and I am also a PhD trained researcher.
16 I would like to speak to concerns about the
17 administration of the functional outcome measures.
18 The briefing document questioned whether the
19 administration of the outcome measures were
20 identical in this trial and the historical control
21 group. As a researcher, I understand the issues
22 surrounding functional outcome measure performance.

1 To raise the stability and quality of clinical
2 trial outcome measures, a group of international
3 experts formed the Adam [ph] training group several
4 years ago. As a member of this group, I have
5 trained evaluators for almost every clinical trial
6 in DMD, including GSK, PTC, Eli-Lilly for DMD,
7 Biomarin, FibroGen, and others.
8 By establishing inter-rater reliability, our
9 training group can ensure consistent training. We
10 go to individual sites to establish reliability
11 with the evaluators and perform quality reviews on
12 video assessments from trials and perform quality
13 reviews on blinded trial data.
14 The lead author on the publication from the
15 Italian natural history study, Elena Mazzone, is a
16 member of our training team. This means that Elena
17 and I present identical trainings on how to conduct
18 functional outcome measures, including when to stop
19 administering the test. We have trained evaluators
20 worldwide, including in Italy and Belgium, as well
21 as at the CINRG sites.
22 I can assure the committee that consistent

1 instructions and encouragement designed to achieve
2 maximum effort are given on every test, regardless
3 if the boy is a clinic patient, in a natural
4 history study, or part of a clinical trial.
5 One of the voting questions is whether
6 decisions to administer the 6-minute walk versus
7 conclusions that the patient could no longer walk
8 were sufficiently objective to allow for a valid
9 comparison. I would like to also alleviate this
10 concern.
11 In the 2011 Italian Natural History
12 publication, the definition given for two boys who
13 were non-ambulant was that they lost the ability to
14 complete the 6-minute walk test but were still able
15 to take a few steps. Able to take more than a few
16 steps is extremely permissive cutoff for being
17 considered ambulant.
18 In comparison, you have been watching the
19 boys on eteplirsen walk up to the podium.
20 Differences of opinion is one explanation of why
21 boys continue to perform assessments longer than
22 the other boys. Superior ability is another. I

1 can personally attest to the quality of my data
2 that you saw presented, and I encourage you to
3 approve the use of eteplirsen.
4 (Applause.)
5 DR. ALEXANDER: Thank you very much. Will
6 speaker number 12 please come to the podium and
7 introduce yourself? Please state your name and any
8 organization you are representing for the record.
9 DR. WAGNER: Good afternoon. My name is
10 Dr. Kathryn Wagner, and I have no financial
11 interest in the outcome of these proceedings. I am
12 a neurologist at the Johns Hopkins School of
13 Medicine and director of the Center for Genetic
14 Muscle Disorders at Kennedy Krieger in Baltimore,
15 Maryland.
16 I have cared for boys and young men with
17 Duchenne for over 15 years. I have 2 patients who
18 participated in the 201/202 study, 4 subjects in
19 the current 301 study, and 3 subjects in the
20 current advanced stage 204 study. None of these
21 9 boys has experienced any drug-related side
22 effects. They are all doing extremely well with

1 their disease.

2 I cannot say that eteplirsen has definitely

3 benefited every boy, but it has benefited most

4 boys. Duchenne is a profoundly disabling and fatal

5 condition without exception. After the age of 13,

6 there's a progressive downward decline.

7 Individual measurements such as the 6-minute

8 walk test may have small day-to-day variabilities,

9 but the course of the disease is consistently

10 downward in the teenage years. Clinically, we

11 rarely see a teenager remain stable over 6 months,

12 and never over 2 years.

13 Yet to highlight just one subject in the 201

14 trial, 006, his 6-minute walk test has remained

15 stable over 4 years with values of 355, 329, 359,

16 332 meters. He is now over 14 years old and still

17 able to rise from the floor. He had no dystrophin

18 at baseline and now has 20 percent dystrophin

19 positive fibers, and 2.47 percent of normal levels

20 by Western blot.

21 If I were this patient's physician, I would

22 see the stabilization of function over years and

1 want the option to prescribe eteplirsen.
2 Muscular dystrophy physicians routinely
3 monitor timed function tests and weigh the risks
4 and benefits of drugs for our patients. We
5 prescribe corticosteroids and follow the rise from
6 floor, run time and/or walk distance, while
7 monitoring the multiple side effects to behavior,
8 bone, and weight, among others. We discuss our
9 findings with the family with whom we make informed
10 decisions whether to continue, reduce, or withdraw
11 a drug.
12 With corticosteroids, we see much less
13 stabilization of function and much more side
14 effects than what has been demonstrated with
15 eteplirsen. From experience with corticosteroid
16 management, the physicians, families, and
17 communities are well-equipped to make individual
18 assessments of benefit of eteplirsen. As a
19 physician, I want the option to prescribe
20 eteplirsen. We cannot withhold a safe drug from
21 even one boy who may benefit.
22 (Applause.)

1 DR. ALEXANDER: Thank you. Will speaker 13
2 please introduce yourself? Please state your name
3 and any organization you are representing for the
4 record
5 MS. NICHOLS: I'm Jodi Nichols.
6 MS. DUMM: Jen Dumm.
7 MS. NICHOLS: Make Duchenne History
8 Coalition arranged our travel. We represent our
9 boys and all families participating in the limited
10 ambulation safety study of eteplirsen. My son,
11 Andrew, is 10 years old. He has been on eteplirsen
12 for one year. I remember watching Andrew begin to
13 walk as a toddler. It was so exciting.
14 Then it was like watching all over again in
15 reverse. As he grew older, Andrew started holding
16 on to furniture, and we had to stabilize and assist
17 him with walking until one day we knew and he knew
18 that he was done walking for good.
19 I find FDA's assertion that kids who are
20 motivated can walk longer than kids who are not of
21 the highest insult. No one was more motivated than
22 my son to keep walking.

1 (Applause.)

2 MS. NICHOLS: But he didn't have the muscles
3 left or the dystrophin available to continue to do
4 so. Then, on April 2nd of last year, Andrew began
5 getting infusions of eteplirsen as part of the
6 limited ambulation study recommended by the FDA in
7 2014. This has given him back capabilities that we
8 thought were gone forever.

9 In Andrew's words, "Today at school, I
10 carried my tray by myself. My arms are stronger.
11 I can wrestle with my brother. I can lift my legs
12 now, and I can almost kick." Today, Andrew crawls.
13 He climbs out of bed into his wheelchair. He sits
14 up independently. Posture and fine motor skills
15 are improved immensely. Andrew has experienced
16 zero negative side effects on eteplirsen.

17 MS. DUMM: My son, 12-year-old John Owen
18 Dumm, shares the same exact story as Andrew. Both
19 Andrew and Owen stopped walking one decade earlier
20 than what is suggested in the FDA briefing
21 documents. Once his infusions started in April
22 2015, new found strength in every muscle is also

1 our new norm. Many in our community can attest to
2 the strength he now exhibits that we all thought
3 was gone forever. You have heard from many of them
4 in our written testimonies.
5 Like Andrew, Owen has experienced zero
6 negative side effects, zero. Before, Owen had
7 difficulty moving his arms. Today, he can feed
8 himself without the use of his mechanical arm. He
9 can write and draw for hours without assistance.
10 He can even hold his own cards when we play card
11 games on game night and move his own pawns in the
12 game Sorry, all because his upper body strength has
13 returned, and not merely because he put his mind to
14 it.
15 While these small improvements might seem
16 like not much to you, but the return of strength is
17 a massive quality of life improvement. We stand
18 before you not just as two fierce mothers. We
19 stand before you representing a patient community
20 that expects you to do your job.
21 We expect you to recognize the safety and
22 effectiveness of this drug. We expect you and the

1 FDA to use the authority and flexibility in FDASIA
2 to approve eteplirsen because it is [mic off].
3 (Applause.)
4 DR. ALEXANDER: Thank you. Will speaker 14
5 please step to the microphone and introduce
6 yourself? Please state your name and any
7 organization you are representing for the record.
8 DR. HEYDEMANN: My name is Peter Heydemann.
9 I am a pediatric neurologist at Rush Medical Center
10 in Chicago. I have been caring for kids in a
11 muscular dystrophy clinic since the early 1980s.
12 Along with our nurses, I have been
13 administering eteplirsen to patient 004 per a
14 university contract with Sarepta. I've also been
15 paid as a Sarepta advisor at times. The Make
16 Duchenne History consortium funded my travel and
17 hotel here.
18 With my few minutes, I want to convey two
19 main points. I have observed unexpected stability
20 in the one boy who I care for, who mirrors the
21 accumulated data of the eteplirsen boys. Secondly,
22 there were no significant side effects.

1 I first observed 004 at age 10 in September
2 2012 after about 9 months of treatment at
3 Nationwide Children's. He was a spirited boy with
4 mild to moderate waddling and a toe walk gait.
5 Based on his style of movement, I thought he would
6 move slower than he did. He took steroids per
7 study requirements, thyroid hormone for
8 hypothyroidism, and last year transiently, he was
9 treated with growth hormone for about 9 months.
10 My expectation initially was that his
11 walking would substantially worsen in the upcoming
12 year and certainly over the next 2 years. What I
13 found was that he continued to move around at about
14 the same speed with little change in his style of
15 walking over those 2 years.
16 It is only in the past year, his fourth year
17 on eteplirsen, that his walking has substantially
18 weakened, especially in the past several months.
19 These degenerative changes are coming much later
20 than I expected.
21 As a side note, I'd like to point out that
22 004 is the only boy I've ever cared for who scored

1 a basket in a school basket game. My functional
2 observations over time were surprisingly favorable
3 compared to my expectations of untreated similar
4 boys, and my observations seemed to correspond well
5 to European natural history group.
6 In terms of adverse events, 004 experienced
7 none, though we had mild laboratory or family
8 observed side effects, which didn't affect him in
9 the least. The weekly medication infusions were
10 made much easier in his case with the use of a
11 permanent intravenous access port, and then with
12 home infusions.
13 In sum, my experience and observations tell
14 me that 004's progressive course of weakness was
15 substantially slowed by eteplirsen without any
16 serious adverse events. I believe that eteplirsen
17 if started in younger DMD boys, with more savable
18 muscle, would improve the course of disease even
19 more.
20 Furthermore, from listening to today's
21 discussion, I believe that eteplirsen meets
22 criteria being reasonably likely to predict

1 clinical benefit, that it's highly unlikely to
2 produce clinical harm, and that dystrophin is
3 produced, and that the many valid criticisms are
4 not negating of any of this but are reasons for
5 further data collection after granting accelerated
6 approval.
7 (Applause.)
8 DR. ALEXANDER: Thank you very much. Will
9 speaker number 15 please introduce yourself?
10 Please state your name and any organization you are
11 representing for the record.
12 DR. CONNOLLY: I am Ann Connolly. I'm a
13 neurologist at Washington University in St. Louis,
14 and I have worked with children and adults with
15 neuromuscular disorders for 27 years. I have been
16 a consultant for Sarepta but stand to gain nothing
17 financially from approval.
18 Please consider what I have to say from the
19 perspective of a clinical researcher in Duchenne
20 dystrophy, a neuromuscular pathologist, and finally
21 with their permission, I speak for Justin and Cole,
22 who I have followed for 3 and a half years in the

1 extension study.
2 I know well the difference between Duchenne
3 and Becker muscular dystrophy as I have cared for
4 more than 150 boys and men with these disorders.
5 If I have a question whether a boy has Duchenne or
6 Becker, I do in fact assess the number of
7 dystrophin positive fibers.
8 In the recent FDA briefing, it was stated
9 that the percent of positive fibers is not a
10 reliable way to quantify dystrophin. Not only do I
11 disagree with you, I ask you to review those
12 biopsies carefully and note that the fibers with
13 dystrophin are larger and more frequent than any
14 biopsy I've ever seen with revertant fibers.
15 I believe these dystrophin fibers are
16 driving the clinical effect. Furthermore, because
17 Justin and Cole are so much stronger than I would
18 have expected, if I met them for the first time
19 today, I would have suggested they have muscle
20 biopsies. When I consider their post eteplirsen
21 biopsies and their physical examinations, I would
22 have reclassified them as having Becker muscular

1 dystrophy. Thus, I do believe that dystrophin
2 positive fibers are a clear biomarker for strength
3 and rescue of muscle.
4 Now, a minute on behalf of Justin and Cole.
5 I have followed Justin since the age of 3 and
6 treated with intermittent twice weekly steroids.
7 However, at the age of 11 when he entered the
8 study, he had difficulty getting off the ground,
9 and I timed him at 26 seconds, and he subsequently
10 lost the ability to get off the ground.
11 Based on all natural history that you and I
12 have reviewed, he should have stopped walking by
13 age 13. At age 16 and a half, after recovery from
14 a femur fracture, he is still walking.
15 My second patient, Cole, was 10 years old
16 when he started the trial and has also done well,
17 despite a fracture at age 11 and a half requiring a
18 cast and no weight bearing for 8 weeks. He has
19 regained the ability to walk and continues to do so
20 at 14 and three-quarters years.
21 They are both exceptionally bright. These
22 two teenage boys do not require someone to feed

1 them, take notes, or take them to the bathroom.
2 While I am a strong advocate of corticosteroids,
3 make no mistake about this fact, corticosteroids,
4 whatever the regimen, do not explain the data here.
5 Be careful of a type 2 error. Thank you.
6 (Applause.)
7 DR. ALEXANDER: Thank you. Will speaker 15
8 please introduce yourself? Please state your name
9 and any organization you are representing for the
10 record.
11 AUSTIN LECLAIRE: Hi. My name is Austin
12 Leclaire. I'm 17 years old. My brother Max has
13 been on eteplirsen for almost five years, and like
14 many in this room, I know what it feels like to
15 watch the drug work and wait for it. After years
16 of waiting, 18 months ago, I was screening for
17 participation in the safety trial.
18 UNIDENTIFIED FEMALE SPEAKER: All right, the
19 video needs to start over please. It wasn't
20 supposed to be played. Can you start the video
21 over please?
22 AUSTIN LECLAIRE: I want you to know that I

1 knew if I didn't perform well, I may not get into
2 the trial, so what you are seeing is my very best
3 effort in the screening, stacking 4 cans, then
4 stacking the fifth can at 48 weeks, and finally
5 lifting my arm over my head at 62 weeks. What does
6 this mean? This means I can now feed myself
7 easier, reach my own urinal, and also transfer
8 myself. This means independence.
9 My brother and I are Duchenne experts.
10 We've lived with it every day. Before Max started
11 eteplirsen, he was on a sharp decline, and I knew
12 he would be soon in a wheelchair because I remember
13 going through that time when I was 9.
14 Brothers may not progress in exactly the
15 same way, but I do know that once you start to
16 decline, you keep declining, it doesn't stop. Max
17 was declining. We were about to get him a
18 wheelchair, and then he stopped. The DMD
19 progress -- it's not normal DMD progress, and I
20 know it because I live through it.
21 I've been on drug 18 months. Normally, boys
22 decline over that time, and I'm not only not

1 getting worse, I'm getting better. I also know
2 that we are making dystrophin.
3 I feel bad that my brother had to go through
4 4 biopsies to prove this over and over again and
5 that data needs to be used now to review the drug.
6 I hear you say that 0.9 percent is disappointing.
7 In order to use a word like that to describe making
8 dystrophin in a disease like Duchenne, I can only
9 guess that you don't know anything about Duchenne.
10 Making 0.9 --
11 (Applause.)
12 DR. ALEXANDER: Please hold your applause.
13 AUSTIN LECLAIRE: Making 0.9 percent is
14 amazing. It lets me feed myself. It keeps Max
15 walking. It gives us a chance. 0.9 percent is not
16 perfect, but it is life changing. My friend, Jake,
17 needs the next drug, exon 45. He has just had to
18 have a painful spinal surgery that I would like not
19 to have to go through because I am on eteplirsen,
20 and my back is much stronger because of it.
21 It's time to listen to the real experts. So
22 to make that easier for you, we brought them all

1 here today. Please use them.
2 (Laughter.)
3 (Applause.)
4 DR. ALEXANDER: Thank you very much. Once
5 again, please hold your applause until the last
6 speaker has spoken. Thank you very much.
7 Will speaker number 17 please introduce
8 yourself? Please state your name and any
9 organization you are representing for the record.
10 DR. GULATI: My name is Neera Gulati, and
11 I'm representing Suneel's Light. I'm presenting my
12 perspective as a physician. The people best able
13 to assess the efficacy of this drug are the experts
14 who have cared for Duchenne patients. Thirty-six
15 doctors who have cared for over 5,000 patients for
16 15 years have presented their support.
17 The FDA is accustomed to evaluating drugs
18 for common highly prevalent diseases such as
19 hypertension and diabetes. Statistically, it is
20 easier to collect data in such diseases. With
21 Duchenne, due to the rarity, heterogeneity, and the
22 shortened lifespan, this is not possible.

1 Statistics are not an adequate tool to
2 assess ultra-rare diseases. Consequently, Congress
3 passed in 2012 FDASIA, a bill I and others in this
4 room supported. In the FDA briefing documents, it
5 was very disappointing for me to read the FDA
6 declared support for FDASIA and yet still insist on
7 data that cannot be collected for a rare disease.
8 Well-controlled studies as interpreted by
9 the FDA are not easily achieved if at all in orphan
10 disease populations. This is not honoring the
11 spirit of FDASIA. Following FDASIA should not be
12 optional.
13 The FDA feels they can better assess disease
14 trajectory based on data they select, and they have
15 discounted specialists' clinical experience rather
16 than valuing the information provided. If I as a
17 family physician inform my patient there is a new
18 drug specialists are recommending for his rare,
19 terminal, life limiting disease that has no
20 significant side effects, but I am not going to
21 give him access to this drug because my
22 interpretation of the data conflicts with the

1 specialist's, I am certain he would leave my
2 practice and seek expert opinion elsewhere,
3 probably from one of those 36 doctors.
4 I have had the privilege to live in Buffalo,
5 New York next to Roswell Park Cancer Institute and
6 witness the prognosis for cancer change from a
7 death sentence to a treatable disease. I watch my
8 patients try treatments with serious side effects
9 that definitely had mortality risks and uncertain
10 benefits. They wanted these options. Why not for
11 Duchenne?
12 In the 1950s, childhood leukemia had
13 100 percent mortality rate. Clinicians such as
14 James Holland from Roswell Park and [indiscernible]
15 Frei from the NCI were convinced medical orthodoxy
16 had it backwards in regards to treating childhood
17 leukemia. They spearheaded novel combination
18 treatments with serious side effects. This was
19 unheard of in the late '50s. Today, combination
20 drug treatments for cancer is standard, and
21 childhood leukemia has a 90 percent cure rate. Why
22 not for Duchenne?

1 It is clear to me the FDA will never feel
2 comfortable with ultra-rare diseases. It is also
3 clear to me from the experts that exon skipping
4 drugs meet the criteria for FDASIA and are worthy
5 of accelerated approval.
6 I am hoping the advisory committee members
7 will have the insight and judgment to realize that
8 eteplirsen should be granted accelerated approval.
9 I'm hoping that FDASIA will be respected and
10 enforced.
11 (Applause.)
12 DR. ALEXANDER: Thank you very much. Will
13 speaker 18 please introduce yourself? Please state
14 your name and any organization you are representing
15 for the record.
16 MS. ARNOLD: Good afternoon. My name is
17 Louise Crow-Arnold, and the Make Duchenne History
18 Coalition paid for my travel today. The diagnosis
19 of Duchenne to a family is devastating. To know
20 that your child, who has just begun to discover
21 things, will gradually have each development taken
22 away is particularly cruel.

1 With no treatments available in the UK, and
2 with the knowledge that if we were to do nothing,
3 his early death would be inevitable, we sought out
4 the most promising, effective, and safest drug that
5 could treat our son, Leon. We moved our family to
6 the United States to take part in the eteplirsen
7 trial.
8 As parents, we had enough faith in the data
9 that was made public to move across the world so
10 that Leon could be in a clinical trial. This huge
11 upheaval has meant we have left our jobs, home, our
12 son's schools, family, and friends behind.
13 Since taking eteplirsen, Leon has shown
14 increasing signs of strength. He performs the
15 Gowers Maneuver far less when rising, and his falls
16 are less frequent. He enjoys drawing and writing
17 far more as he tires less with these activities,
18 and his hand grip has strengthened.
19 His stamina has increased, and he can cover
20 greater distance before fatigue sets in. His
21 stroller is staying in the garage far more than
22 when we arrived in America eight months ago. Our

1 biggest reward is that Leon can hug us tighter.
2 At no point have we experienced any side
3 effect with eteplirsen, either during the infusion,
4 afterwards, or at any time during the week between
5 doses. When Leon was born, we stared at our
6 sleeping child in wonder, and it is then as a
7 parent that you vow you will always love them and
8 do anything you can for them.
9 That is why we have moved halfway around the
10 world. That is why we are here today, for Leon,
11 and for every other child who has the misfortune to
12 be born with Duchenne.
13 This drug is not a false promise. We have
14 witnessed the efficacy of this drug. We are not
15 just desperate parents, as often described in the
16 media. We have listened to our doctors. Standards
17 of efficacy matter, but flexibility matters too.
18 Eteplirsen patients are experiencing delayed
19 loss of motor milestones. The data is sufficient
20 to approve eteplirsen, and the FDA has the
21 authority to grant approval. Thank you.
22 (Applause.)

1 DR. ALEXANDER: Thank you very much. Will
2 speaker 19 introduce yourself? Please state your
3 name and any organization you are representing for
4 the record.
5 MS. EICHELBERGER: My name is Kim
6 Eichelberger, and my son Cole has Duchenne. Our
7 travel was paid for by the Make Duchenne History
8 Coalition. In August 2011, when Cole was 10 years
9 old, he was selected as one of 12 participants in
10 the eteplirsen 201 trial. He was selected because
11 he appeared to be on the cusp of decline.
12 He walked with lordosis to compensate for
13 quadriceps weakness. He had a wide stance because
14 he needed the support, and he had the typical
15 Duchenne waddle when he walked. In short, he did
16 not look like a child who would be walking for
17 years to come.
18 We now know that for the first 24 weeks he
19 received placebo. During this time, he declined
20 significantly in his 6-minute walk, then he started
21 eteplirsen. The FDA's briefing documents argue
22 that boys on eteplirsen are progressing exactly as

1 one would expect given the natural history of the
2 disease. They argue that several of the boys have
3 reached distances on the 6-minute walk that would
4 suggest they will come off their feet shortly,
5 signaling the drug doesn't work.
6 My son is one of those referenced boys. At
7 the 3-year mark, my son walked right around
8 100 meters on the 6-minute walk test. Six months
9 later, at the 3 and a half year mark, he walked
10 only 50 meters on the 6-minute walk test. Any
11 clinician will tell you based on that trajectory
12 that his walking days were numbered. And then
13 6 months later, at the 4-year mark, my son still
14 walked 50 meters on the 6-minute walk test. And
15 then just a few weeks ago, at the 4 1/2 year mark,
16 my son not only completed the 6-minute walk test
17 once again, but after the visit, he informed us he
18 had walked further than he had on the previous two
19 visits, walking further than he had on the test in
20 over a year.
21 I'll say that again because it needs to be
22 heard. At 14 and a half years old, instead of

1 coming off his feet like the briefing documents
2 predicted would happen, my son improved his
3 distance on the 6-minute walk. His is not the
4 story of a Duchenne outlier who continues to
5 perform better than one would expect. His is the
6 story of a Duchenne patient who was falling off the
7 cliff toward irreversible decline and was somehow
8 yanked back onto the ledge.
9 I should also mention, because it is in the
10 briefing documents, that Cole has never had an
11 intensive physical therapy regimen. In fact, over
12 the last 4 and a half years, he has received
13 physical therapy for a total of about 6 months. In
14 addition, his steroid dose has remained at roughly
15 half of the weight recommended dose of
16 0.9 milligrams per kilogram.
17 Cole will enter high school this year still
18 on his feet, which is something my husband and I
19 could not have imagined possible when we were given
20 his diagnosis. I can say with confidence that the
21 life my family is living would be very different
22 than it is today were it not for eteplirsen.

1 I believe if you were to ask his doctors,
2 Drs. Ann Connolly and Jerry Mendell, both of whom
3 are here today, that they would agree. In fact
4 you've just heard Dr. Connolly's opinion on Cole's
5 progression.
6 This drug should be granted accelerated
7 approval so that anyone who can be helped by it has
8 access and can benefit the way Cole has while we
9 wait for definitive answers from the confirmatory
10 trials. Thank you for the opportunity to speak
11 today.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker 20 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.
17 MS. ELLSWORTH: My name is Terri Ellsworth
18 from Pittsburgh, Pennsylvania, and my son Billy,
19 age 15, has been receiving eteplirsen since August
20 2011, receiving 30 mgs/kg of the drug. The Make
21 Duchenne History Coalition arranged for our travel.
22 Instead of spending the most important

1 3 minutes of my life talking about Billy's
2 accomplishments and success on eteplirsen, I have
3 to spend it talking about the misleading briefing
4 documents that were released by FDA's neurology
5 division.
6 In these documents, FDA states that boys on
7 eteplirsen, quote, "Appear to receive optimal care,
8 including intensive physical therapy and intensive
9 steroid regimens," close quote, claiming that PT
10 and steroids are responsible for these boys'
11 stability rather than the eteplirsen.
12 We want the panel to know that the Columbus
13 trial family strongly disagree with these comments.
14 Our boys either received minimal, standard, or no
15 PT throughout the trial. In addition, most of the
16 boys on eteplirsen are massively underdosed with
17 steroids.
18 My son spent the entire trial at
19 21 milligrams of deflazacort, which is nearly half
20 the recommended dose. The advisory committee
21 process is supposed to be an unbiased panel, but
22 with the FDA's briefing package, the committee has

1 been tainted and led astray with misrepresentation
2 in the information that they received.
3 I read posts daily on social media from
4 fellow Duchenne parents about their daily
5 caregiving and challenges that their boys face. I
6 read it, I understand it, I get a lump in my
7 throat, but that is not my life. I don't wake
8 several times a night to turn my son in bed, he
9 turns himself.
10 I don't have to feed my son, he feeds
11 himself, and then carries his dishes and glass to
12 the sink. I don't have to brush my son's teeth, he
13 does it himself. I don't dress my son, he dresses
14 himself, and then comes down the stairs for
15 breakfast. I don't bathe my son, he does it
16 himself.
17 Billy was not and is not an outlier. Before
18 eteplirsen, Billy was an extreme toe walker. He
19 consistently walked with his heels 3 inches off the
20 ground, which typically indicates the end of
21 ambulation is near. Now, almost 5 years later, he
22 is still walking, and his heels are much closer to

1 the ground. This is not placebo effect, this is
2 eteplirsen still at work.
3 MR. ELLSWORTH: My name is Billy, and I have
4 been receiving the eteplirsen drug since I was
5 10 years old. You should approve eteplirsen
6 because I am very strong and still walk a lot. I'm
7 afraid that if you don't approve this drug, I will
8 become very weak and not be as independent like I
9 am now. It makes me sad and afraid that I won't be
10 able to do all the things that I can do now.
11 I see other boys my age and younger that
12 cannot do what I can do, and it makes me mad that
13 they also cannot have the drug. I hardly ever have
14 to ask my parents to help me with anything because
15 I can do most everything in my daily life by
16 myself.
17 I'm going to beat this bloody disease, but I
18 need your help. So please help me and my friends
19 and do the right thing. FDA, please don't let me
20 die early.
21 (Applause.)
22 DR. ALEXANDER: Thank you very much. Once

1 again, please hold your applause until the final
2 speaker has spoken.
3 Will speaker 21 please introduce yourself?
4 Please state your name and any organization you are
5 representing for the record.
6 (Applause.)
7 MS. MILLER: My name is Debra Miller. I'm
8 the founder and CEO of CureDuchenne, which has paid
9 for my travel. CureDuchenne provided funding to
10 Sarepta in 2010 to conduct studies that enabled it
11 to get off clinical hold and move into human
12 clinical trials for eteplirsen.
13 Duchenne, unlike other neuromuscular
14 diseases such as MS, has no ebbs and flows or
15 remissions, only a downward trajectory of loss
16 first of ambulation, then autonomy, and ultimately
17 life. Our kids have been taking steroids, which
18 carry multiple side effects and have uneven
19 benefits. Fortunately, we've been able to use
20 off-label steroids or buy them from other
21 countries, otherwise our children wouldn't not have
22 been able to benefit from them.

1 Exon skipping works. It may not be the
2 complete cure, but it helps many boys extend
3 ambulation and improve their quality of life. We
4 cannot buy it off-label or order it from another
5 country. Your approval is our only hope for
6 access. The current exon skipping trials were
7 designed many years ago with limited knowledge of
8 Duchenne's natural history.
9 You, the FDA, can insist on a perfectly
10 designed trial and sacrifice this current
11 generation of Duchenne boys, or you can allow
12 access to these drugs while we perfect clinical
13 trial designs for the future.
14 CureDuchenne has sponsored cTAP, the first
15 collaboration between biotech and pharma companies
16 created to apply statistical analysis to understand
17 the natural progression of Duchenne and design more
18 informed clinical trials.
19 We encourage the FDA and sponsor companies
20 to take advantage to cTAP and meanwhile use the
21 accelerated approval program to allow the use of
22 eteplirsen. Use your power to remove the drug if

1 it is demonstrated to be unsafe or ineffective
2 post-marketing.
3 To cure Duchenne, we will need a combination
4 of therapies to treat the whole disease. Exon
5 skipping is a cornerstone of this approach.
6 CureDuchenne is funding the development of multiple
7 drugs, but we cannot test drug combinations until
8 the first drugs are approved.
9 I have a son with Duchenne. His name is
10 Hawkin. He is 19 years old and just finishing his
11 freshman year at USC. He's a news editor for the
12 Daily Trojan. He lives independently without an
13 aide. Although he uses a scooter or power chair
14 for distance, he is able to walk and take care of
15 himself and drive his friends around town.
16 He has approximately 3 percent of normal
17 dystrophin. Even small amounts of dystrophin can
18 add years of independence and improve quality of
19 life, but we need to start treatment when they are
20 young to realize the true benefit.
21 I respect the FDA's caution in setting a
22 precedent in approving new drugs, but our kids are

1 not a precedent, they are real live human beings
2 and they are short on time.
3 An FDA official once told me, "The worst
4 thing we can do is approve a drug and then have to
5 pull it off the market." I argue that the worst
6 thing you can do is deny access to a drug and then
7 find out it works too late, after we have lost a
8 generation of boys. Thank you.
9 (Applause.)
10 DR. ALEXANDER: Thank you very much. Will
11 speaker 22 please introduce yourself? Please state
12 your name and any organization you are representing
13 for the record.
14 MS. McSHERRY: Hi. My name is Jordan
15 McSherry. Today, I'm introducing my brother,
16 20-year-old brother, Jett McSherry's video
17 testimony. This video was filmed in his college
18 dorm room. So feel free to laugh. Audio.
19 (Video played and transcribed.)
20 MS. McSHERRY: [Indiscernible] I feel
21 pretty -- I've noticed a few changes since
22 [indiscernible]. I started to take eteplirsen in

1 October of 2014. Right now, it's April 2015, and
2 I've been on it for around about 20 weeks now.
3 I feel pretty -- I've noticed a few changes
4 since I've -- since I've been on this drug. I've
5 noticed that I have more strength than I usually
6 have. I can do more stuff on my own. I can eat by
7 myself a lot easier.
8 I sleep a lot better at night. I don't
9 snore as much anymore. I don't get tired as
10 easily. I don't feel so tired at the end of the
11 day [ph] than I did before. I can also open cans
12 myself, which I couldn't do before pretty easily.
13 AIDE: I've been working with Jett since the
14 beginning of the school year, and one thing that
15 I've noticed [indiscernible] better since he's been
16 on the drug was at first his snoring was really
17 bad, right, could barely fall asleep at first and
18 then after [indiscernible] once he got on the drug,
19 I'd have to say right around probably December,
20 winter break, around that area, he just got a lot
21 better and it's -- I mean every one snores but it's
22 not nearly as bad as it's ever been and it seems to

1 be improving every day.
2 Another thing with him sleeping is he likes
3 to put his leg up when he sleeps but that's
4 something that he asks me to do for him. And then
5 one time I woke up in the middle of the night and
6 he had his leg up himself and he did it himself
7 without anyone asking.
8 Just little things like he used to ask me to
9 get him food, and when he needed food I'd either
10 have to help feed him or open the bag like chips
11 but now he can open a bag of chips by himself.
12 Another example is this water bottle, I used to
13 have to feed him the water bottle, but now he can
14 for the most part grab it himself and put it up to
15 his mouth, but also I can leave it on the desk and
16 he can just come over and grab it by himself.
17 (Laughter.)
18 AIDE: [Indiscernible] And also other
19 things like his laptop, he can -- if I left his
20 laptop on the desk [indiscernible] controller or
21 the video game controller I can just leave it right
22 there and then he -- [mic off].

1 (Applause.)
2 DR. ALEXANDER: Thank you very much. Will
3 speaker 23 please introduce yourself? Please state
4 your name and any organization you're representing
5 for the record.
6 MS. SECKLER: My name is Tracy Seckler, and
7 my son Charlie has Duchenne. I'm the cofounder of
8 Charlie's Fund, a public charity that has directed
9 $38 million since 2004 into a varied portfolio of
10 medical research and drug development programs,
11 including exon skipping and other therapeutic
12 approaches.
13 Here's a fact that is not in dispute today,
14 not in the medical literature, not in the FDA
15 briefing documents, not among the experts, and not
16 in our personal experience. Two clear warning
17 signs let us know that loss of ambulation is coming
18 soon. When a boy loses the ability to
19 independently rise from the floor, he is highly
20 likely to lose ambulation in 1 to 2 years. And
21 scores of 13 and 9 on the North Star Ambulatory
22 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.

1 One boy lost the ability to rise from the
2 floor 3 years ago, yet today he can still walk.
3 Another lost the ability to rise from the floor
4 2 years ago; today, he can still walk. A third boy
5 lost the ability to rise from the floor a year and
6 a half ago; today, he's still walking.
7 A look at the North Star scores provides
8 more evidence that these boys should have lost
9 ambulation by now. The three kids who dropped
10 below a score of 13 more than 2 years ago are still
11 on their feet, and the 4 who dropped below a score
12 of 9 more than a year ago, still walking.
13 These boys are deviating significantly from
14 their natural history counterparts who were
15 rigorously selected to provide the closest possible
16 match. Importantly, they are also defined their
17 own predicted natural history based on uncontested
18 signals of rate of disease progression.
19 Later today, you will be asked to consider
20 several questions. Theoretical concerns about the
21 limitations of natural history notwithstanding,
22 this data provides the information you need to

1 answer questions 5 and 6. As for question number
2 7, these boys are the answer. These boys are the
3 substantial evidence of eteplirsen's treatment
4 effect. Thank you.
5 (Applause.)
6 DR. ALEXANDER: Thank you very much. Will
7 speaker number 24 please introduce yourself?
8 Please state your name and any organization you're
9 representing for the record.
10 MS. McNARY: My name is Jenn McNary. My
11 travels were supported by the Make Duchenne History
12 Coalition, and this is Max. I am told that I was
13 the first person that knew the drug now called
14 eteplirsen worked, before any of the data was
15 released.
16 It's not because I'm a scientist or a
17 clinician, it's because one of my sons, Max, was
18 one of the first boys in the U.S. to receive the
19 drug. His older brother, Austin, who you've heard
20 from, had already stopped walking at 10 and a half
21 years old. He was unable to get into the trial
22 because he was unable to walk, forcing me into a

1 situation where there was essentially an open
2 placebo-controlled trial in my own home.
3 At trial start, Max was 9 and a half and on
4 a downward spiral. It was Austin who told me at
5 the time, "Max is falling a lot, Mom. I think he
6 needs a power wheelchair." We ordered one. The
7 FDA states in their briefing document that there's
8 a wide range of loss of ambulation for boys
9 amenable to exon 51 from 8 to 18 years.
10 Those in this room who know Duchenne know
11 most lose ambulation between 10 and 12 years. So
12 why is the FDA so focused on outliers? Our sons
13 were not chosen for the trial because they are
14 outliers, they were typical boys. The boys in the
15 study were chosen because they were declining,
16 typical for Duchenne, until they began the
17 treatment with eteplirsen. This is when their
18 progression became atypical.
19 I was skeptical at first because the trial
20 was blinded and placebo-controlled. I didn't even
21 know if Max was on drug, until the day that I knew.
22 Max opened a milk container at the airport for the

1 first time. His grip has always been weak. He
2 always handed the jug to me to open, but that day
3 he opened it. Small changes turned to bigger
4 changes over time.
5 Max was choosing to ride in his wheelchair
6 less and less until he decided not to use it at
7 all. He was not coming home from school tired,
8 despite abandoning the chair. It had been with him
9 daily since kindergarten. He started participating
10 normally in gym class. And most importantly, he
11 totally stopped collapsing. We cancelled that
12 order for a power chair, and 4 and a half years
13 later, we haven't seen the need.
14 Max is still declining some. Over 4 years,
15 his walk test has remained about the same, which in
16 itself is amazing to have this kid just dangling on
17 the edge of a cliff and stay there for 4 years
18 without falling off.
19 But more importantly, Max's daily life and
20 level of independence has changed. Last week,
21 14 and a half-year-old Max got out of his bed. He
22 got dressed. He put on his shoes and his backpack

1 and he walked out to the school bus unassisted.
2 I am incredibly proud to be standing here
3 saying the same thing I've been saying daily since
4 day 1, eteplirsen works. Only today, I'm happy to
5 be surrounded and supported by sound dystrophin and
6 clinical data, physician, researcher, and patient
7 testimonies similar to my own.
8 I want to impress upon the panel that a
9 recommendation for approval is the only acceptable
10 outcome of today's meeting. And if you ask me,
11 it's incredibly overdue at this point. We are the
12 lucky ones, the boys in orange. So many are still
13 waiting. Let's do the right thing.
14 (Applause.)
15 DR. ALEXANDER: Thank you very much. Will
16 speaker 25 please introduce yourself? Please state
17 your name and any organization you are representing
18 for the record.
19 DR. PARTRIDGE: Yes, I'm Terry Partridge,
20 and I'm currently professor of systematic
21 integrative biology at George Washington medical
22 school here in DC. Before that, I was in London

1 where for about the past 45 years, I've worked on
2 research on muscular dystrophy, and I was head of
3 the Medical Research Council Clinical Sciences
4 Centre muscle group.
5 My main area of interest is the mechanisms
6 of muscle repair and of exon skipping, and I think
7 the two are beginning to become involved with one
8 another. One of the problems that came up today,
9 regularly, was the inconsistency about dystrophin
10 measurement between different studies, and across
11 time, and within the same manual, and between
12 muscles. And I think there's a perfectly good
13 explanation to this, which I think should be taken
14 into account when considering the data.
15 On the screen at the moment is an old slide
16 from Francesco Muntoni's original systematic trial
17 showing perfectly good post-dystrophin, pre-
18 post-dystrophin differences there. One of those is
19 slightly more overloaded than the other, but it's
20 good data. And it shows that there is dystrophin
21 there. And the question is, what does it do?
22 So the problem with the exon skipping is

1 that it works on very small groups of muscle cells.
2 When you look at these biopsies, and I was hoping
3 to put one up, you find tiny groups of muscles,
4 muscle fibers that are affected. These are about a
5 millimeter cubed in size. And if you were to try
6 to find those with the 10 or 20 micrograms of a
7 muscle biopsy, you might find two or three of those
8 in one of your biopsies, in which case you'd find
9 dystrophin, or you might miss all of them, in which
10 case you wouldn't find any dystrophin. And I think
11 this accounts for quite a lot of the lack of
12 consistency.
13 I see I'm running out because my slides are
14 not working. So the other thing I would say is
15 that you need to have something more easily
16 evaluable than the amount of dystrophin that's
17 present. You need to use biomarkers that are
18 beginning to come up that are much less invasive,
19 like urinary proteins that are lost from muscle
20 during the stages of degeneration and regeneration.
21 And you can show quite easily, as I would be doing
22 if the slides were working, that there is a -- it's

1 too late -- that there is a distinctive benefit.
2 Can I go back to that slide or not? Yes. .
3 The last one, that's it. I've lost it. I don't
4 know. [Off mic.}
5 DR. ALEXANDER: I'm sorry. Can you
6 extend -- can you turn on the microphone, please,
7 so the gentleman can have just a second or two more
8 for his comments?
9 (Applause.)
10 DR. PARTRIDGE: So these two slides up there
11 show basically following two proteins in the urine
12 that are lost from muscle fibers when they're
13 damaged, and it shows the effects of a morpholino
14 treatment in the mouse to skip the exons and
15 restore dystrophin. And it shows that -- can you
16 go on to the last one again?
17 Yes, that's the one. It shows that with the
18 treatment, the lower of those curves, in both
19 sides, the treatment takes down those biomarkers in
20 the urine. These are easily accessible biomarkers.
21 They're the same biomarkers as are being used in
22 Duchenne boys, and they would, I'm sure, form the

1 basis of any trial should the committee agree to an
2 accelerated approval for the continuation of
3 eteplirsen.
4 DR. ALEXANDER: Thank you very much.
5 (Applause.)
6 Will speaker 26 please introduce yourself?
7 Please state your name and any organization you are
8 representing for the record.
9 MR. BOWER: Hello. My name is Caden, and
10 I'm one of the 12 boys in Sarepta's eteplirsen --
11 DR. ALEXANDER: Can you speak into the
12 microphone a little bit more, please?
13 MR. BOWER: I ask that you please approve
14 this medicine. If it is not approved, I am scared
15 that I will lose the ability to walk, and I don't
16 want this to happen to me. This medicine is
17 keeping me walking and allowing me to keep up my
18 day-to-day activities and remaining stable. Thank
19 you.
20 MS. PEREZ: Hello. My name is Beth Perez,
21 and the Make Duchenne History Coalition paid for
22 our travel. And my 12-year-old son is one of the

1 12 boys in Sarepta's study. You heard it from him,
2 it is keeping him walking, and he is here standing
3 next to me today.
4 Caden has faithfully devoted nearly five
5 years of his life to this exon skipping drug. He
6 has not been on placebo and has been receiving
7 50 milligrams of the drug throughout the study.
8 Eteplirsen is giving my son a fighting
9 chance. I would have expected him to have more of
10 a physical decline by this stage of his life, and I
11 feel that he would be completely non-ambulatory if
12 it weren't for this life-saving drug. It is safe
13 and effective with zero side effects.
14 One thing I can tell you is that through
15 receiving these eteplirsen treatments, he is able
16 to live a more functional life than that of a
17 12-year-old DMD patient not receiving the drug.
18 For example, a typical DMD boy cannot pedal a
19 bicycle, but Caden is remarkably able to pedal a
20 few feet on a therapeutic tricycle and has less
21 falls since receiving the drug.
22 Caden is receiving below the recommended

1 dose of steroids. Until October 2015, he was on
2 18 milligrams of deflazacort. At that point,
3 Dr. Mendell increased the dose to 24 milligrams.
4 Caden does not receive any intensive
5 physical therapy. He receives therapy as advised
6 for any child with DMD. Caden's therapist has seen
7 and said that he has increased endurance for
8 walking activities without the need of assistive
9 devices.
10 He has participated in aquatic therapy
11 sessions for longer periods without excessive rest
12 breaks, and he has shown drastic improvements in
13 his active range of motion, most notably in his
14 hamstrings and hip flexors.
15 As parents, it's difficult seeing your child
16 struggle, but to witness them tackle life's
17 seemingly simple daily tasks is a heartbreaking
18 battle that any DMD parent can relate to. I don't
19 know want to tell my son that his dreams for a
20 future are going to be taken away from him.
21 The boys fighting DMD are the strongest
22 warriors that I know of, and if this drug helps to

1 make their world a little easier to live, then I
2 don't see any ethical reason as to why this
3 medicine should not be approved.
4 We support Sarepta and eteplirsen one
5 hundred percent. This drug means a future and a
6 promise to my son, our family, and every Duchenne
7 boy. Thank you for your time.
8 (Applause.)
9 DR. ALEXANDER: Thank you very much Will
10 speaker 27 please introduce yourself? Please state
11 your name and any organization you are representing
12 for the record.
13 DR. MICELI: I'm Carrie Miceli, professor of
14 microbiology, immunology, and molecular genetics
15 and co-director of the Center for Duchenne Muscular
16 Dystrophy at UCLA. For the past 10 years, my own
17 laboratory has been well funded to explore
18 mechanisms for boosting the activity of morpholino
19 directed DMD exon skipping in mouse and human
20 models. I'm familiar with measuring and
21 interpreting expression of skipped dystrophin
22 proteins.

1 One stated concern relates to the fact that
2 the pre-treatment control tissues was exhausted,
3 and thus controls from the PROMOVI pre-treatment
4 biopsies were included in analysis of biopsy 4
5 challenging interpretation.
6 It's important to note that two patient
7 pre-treatment samples were included in both
8 assessments of biopsies 1 through 3 and biopsy 4 by
9 immunohistochemistry. These samples should serve
10 as internal controls that allow for the validation
11 of the new set of controls, as typical of the
12 treatment cohort. The findings are interpretable
13 and clearly support induction of dystrophin.
14 Exon skipping uses morpholino and is known
15 to induce patchy dystrophin expression. Therefore,
16 assessment of eteplirsen induced dystrophin
17 requires consideration of both the absolute amount
18 of dystrophin present as well as its distribution.
19 Given the level and distribution of induced
20 dystrophin being observed, it's reasonable to
21 expect that some positive fibers express as much as
22 5 to 12 percent of normal dystrophin, levels

1 clearly predicted to impart some production of
2 myofiber's contraction induced damage.
3 Data from studies in BMD and DMD patients
4 and in mouse and canine models support the
5 suggestion that relatively low levels of dystrophin
6 can be functionally significant even if only
7 expressed in a limited number of fibers.
8 Of note, the number of dystrophin positive
9 fibers is not expected to be equal to the percent
10 of normal dystrophin protein unless each fiber
11 expresses 100 percent of normal levels of
12 dystrophin, which is clearly not the case. There
13 is no inconsistency there.
14 In response to the first set of briefing
15 documents, 36 prominent scientists and physician
16 experts in Duchenne provided FDA with a letter
17 clarifying issues raised. We ask that the letter
18 be made available unredacted to the advisory
19 committee. If you have not seen it in its
20 entirety, we hope you can gain access today.
21 Quoting from that letter, "We conclude that
22 there is strong evidence of induced dystrophin

1 production upon prolonged eteplirsen exposure."
2 The letter goes on to say, "The findings of this
3 trial are sufficiently robust to support the
4 proposed mechanism of action of eteplirsen to
5 provide a plausible explanation for the relative
6 gain in function observed within the treatment
7 group, and serve to bolster confidence that there's
8 a positive treatment effect."
9 I am also the mother of Dillon Miceli Nelson
10 who lives with Duchenne. Given the strong safety
11 profile, I'd be keen for Dillon to be on this drug
12 if it were pertinent.
13 (Applause.)
14 DR. ALEXANDER: Thank you very much. Will
15 speaker 28 please introduce yourself? Please state
16 your name and any organization you are representing
17 for the record.
18 MS. KELLY: Hi. My name is Wendy Kelly, and
19 I'm here today with Susan Patterson. The Make
20 Duchenne History Coalition arranged our travel.
21 We're here today to speak about our children's
22 experience on eteplirsen and how our sons have been

1 performing everyday activities easier since
2 starting the drug.
3 My 8-year-old son, Jackson, has been on
4 eteplirsen since January 2015. Susan's 8-year-old
5 son, David, has been on eteplirsen since July 2015.
6 Both of our boys are part of the confirmatory trial
7 that was clearly guided by the FDA in the April
8 2014 guidance. In that guidance, FDA also guided
9 for eteplirsen safety trials on younger Duchenne
10 patients and those at later stages of the disease.
11 Since they started on eteplirsen last year,
12 our boys have stabilized and they have started
13 doing things that they could not do before,
14 everyday things that normal 8-year-old boys take
15 for granted, like opening car doors, getting off
16 the floor with ease, easily bending over to pick up
17 things off the floor. We truly believe that
18 eteplirsen has changed the trajectory of their
19 disease.
20 Our children may have a future now that
21 might give them the opportunity to walk well into
22 their teens. With that ability comes independence

1 that most boys living with Duchenne lose very
2 quickly after going into a wheelchair.
3 Our observations verify and confirm what
4 Sarepta's data on the original 12 patient study
5 show, that treatment of eteplirsen can cause a real
6 and concrete impact on the lives of Duchenne
7 patients.
8 In addition, it is necessary to note that
9 neither of our boys have experienced a single
10 negative side effect from being on eteplirsen.
11 This drug has our stamp of approval. We believe it
12 is unfair of the FDA to make a comparison to Becker
13 muscular dystrophy. The comparison should be to
14 Duchenne. Eteplirsen is allowing our boys to
15 produce dystrophin.
16 We would love to turn our sons' Duchenne
17 into Beckers, but that should not be the standard
18 of measurement. Any benefit that allows our boys
19 to walk longer, breathe longer, or just make it
20 through the day is worthwhile.
21 The only reason our children were able to
22 receive eteplirsen is because the FDA allowed for

1 confirmatory trials in their 2014 guidance to the
2 company. By the time these confirmatory trials are
3 complete and the data is analyzed, it could be
4 another three years.
5 The human cost of not approving this drug
6 now and waiting up to three years for confirmatory
7 trials to be complete would be massive. Children
8 will have lost the ability to walk, to pick
9 themselves up off the ground, and to feed
10 themselves.
11 We all know what the end result of Duchenne
12 is, and the patient testimony here today should
13 tell you all that you need to know, the benefit of
14 eteplirsen far outweighs its risks. From the
15 Pattersons and the Kellys, please approve this
16 drug.
17 (Applause.)
18 DR. ALEXANDER: Thank you very much. Will
19 speaker 29 please introduce yourself? Please state
20 your name and any organization you are representing
21 for the record.
22 MR. LEFFLER: My name is Mitch Leffler. The

1 Make Duchenne History Coalition arranged my travel
2 here today, and I have a 12-year-old son who has
3 been on drisapersen and is now on eteplirsen.
4 The decision we're facing today would be an
5 easier one if we had a large placebo-controlled
6 data set, but here's the problem with collecting
7 that data set for exon 51. We're already starting
8 with an orphan disease. Then you remove the
9 87 percent of patients that aren't amenable to this
10 exon skip.
11 Out of the remaining 13 percent, you take
12 away the one-third of boys who are too cognitively
13 affected. Then you need to remove the boys who
14 have already participated in an exon-skipping trial
15 and are no longer drug naïve. Then you subtract
16 the families that live too far from a study site to
17 travel once per week. Then we lose the families
18 that have chosen to participate in a less demanding
19 clinical trial.
20 Then you subtract the families that cannot
21 afford clinical trial participation. For example,
22 my own family has spent over $40,000 in childcare

1 and lost wages to participate in two clinical
2 trials.
3 Lastly, you need to subtract the boys that
4 do not fit the inclusion criteria, that are too old
5 or too young, their pulmonary or cardiac function
6 isn't strong enough, or maybe it's something as
7 simple as elevated white blood cell count during
8 the screening. But they may not fit in the narrow
9 6-minute walk criteria that's necessary to show a
10 treatment effect over a shorter period of time.
11 The result is that you're left with so few
12 boys that you end up relaxing the enrollment
13 criteria in order to get the numbers. And once
14 that happens, if you're using the 6-minute walk,
15 you've introduced so much variability into your
16 trial that you've changed science into
17 randomization roulette.
18 Some may say extend the duration of the
19 trial, keep children on placebo for a longer period
20 of time, but this trial includes muscle biopsies
21 under general anesthesia. If you think that
22 procedure is minor, you should know that my son has

1 a permanent limp from his two muscle biopsies in
2 his quadriceps.
3 So once you introduce this kind of
4 procedure, absolutely a more minor increase over
5 minimal risk, you have to involve the prospect of
6 direct benefit for every participant, a requirement
7 that is not satisfied by participation in a placebo
8 arm.
9 So we all know that a large scale,
10 long-term, placebo-controlled trial would give us
11 some of the answers we're looking here today. But
12 here's the deal. We can't have one. It's not
13 numerically possible, and according to FDA's own
14 guidelines on pediatric clinical trials, it is not
15 ethical.
16 So when we can't have the optimal data we
17 want but we still need to make a decision, what do
18 we do? Do we abandon a promising treatment or do
19 we become more interested in getting at the truth
20 than focusing on methodological concerns?
21 That is a question we're answering today,
22 and it's a question that's going to be asked more

1 and more often with genetic targeting of rare
2 diseases. The world's leading experts are here
3 today telling us that what they're seeing is
4 unusual. Our boys are changing in front of our
5 eyes. It can't be ignored. It can't be explained
6 away. And it needs to be acknowledged today.
7 Thank you.
8 (Applause.)
9 DR. ALEXANDER: Thank you very much. Will
10 speaker 30 please step to the podium and introduce
11 yourself? Please state your name and any
12 organization you are representing for the record.
13 MR. WESLEY: Yes, Mr. Chair, my name is
14 Keith Wesley. Make Duchenne History Coalition paid
15 for my lodging. My son, Jake Wesley, is 15 years
16 old, has Duchenne muscular dystrophy. Jake's not
17 in any current clinical trial. Jake's lack of
18 abilities and limitations due to the unfortunate
19 circumstances are what have brought me before you
20 today. I have slides but they're not coming up.
21 Oh, here you go.
22 DR. ALEXANDER: And I believe you have

1 control of the slides or no?
2 MR. WESLEY: Yes, they are up now. Thank
3 you.
4 DR. ALEXANDER: Very good.
5 MR. WESLEY: Jake lost the ability to walk
6 at 8 years old. After being confined to a
7 wheelchair for several years, Jake developed severe
8 neuromuscular scoliosis, a condition that occurs in
9 a large majority of the boys with the more severe
10 phenotype, those boys that produce little or no
11 dystrophin.
12 Jake underwent an extremely invasive 10 and
13 a half hour spinal fusion surgery this past year.
14 I'd like to draw your attention to those photos.
15 Earlier today scoliosis was mentioned. Here it is.
16 And while pictures tell a thousand words, they
17 don't tell you the fear that these boys endure for
18 months in advance of this surgery.
19 Although Jake is not in the eteplirsen
20 trial, his best friend, Austin Leclaire, is. Jake
21 and our family have known Austin for almost
22 10 years. Prior to Austin being in a trial, his

1 motor skills almost mimicked Jake's. Now Austin
2 can lift his hand above his head. And prior to
3 Jake's surgery he contacted a number of boys with
4 DMD who had spinal fusion surgery.
5 The majority of these boys said their
6 biggest regret was the fact they could no longer
7 feed themselves. It seems like such a small thing
8 to ask, the ability to feed yourself, but to these
9 boys, it means the world.
10 While Austin has regained the ability to
11 raise his arms above his head and transfer to bed
12 independently, Jake can no longer feed himself.
13 While Austin has regained the ability to toilet
14 independently, Jake completely is dependent on us
15 for all his personal care. After years of
16 progressing identically, there should be no reason
17 that Jake and Austin would start to differ in
18 progression unless the drug works.
19 I'm an elected official in the state of
20 Pennsylvania, and I ran for office because I wanted
21 to make a difference. I didn't just want to make a
22 difference, I did make a difference. I like to

1 believe the same of all of you. Why else, if not
2 to make a difference?
3 In closing, my intent is what Congress
4 wants, and voiced through FDASIA, and that is to
5 deliver safe and effective drugs for the treatment
6 of rare and severely life-threatening diseases. I
7 don't know a better candidate for accelerated
8 approval than a drug that apparently its only side
9 effect is extended life.
10 (Applause.)
11 DR. ALEXANDER: Thank you very much. Will
12 speaker number 31 please introduce yourself?
13 Please state your name and any organization you are
14 representing for the record.
15 MR. VAISH: Hi. My name is Ryan, and I have
16 Duchenne. I am 13 years and 10 months old, and I
17 have been on eteplirsen for almost five years
18 without missing a single dose. Ever since I was
19 diagnosed, all the doctors are saying by the time
20 I'm 13, I would be in a wheelchair and not be able
21 to do things I can do now. But since I've been on
22 the medicine, I am still walking, swimming, playing

1 with my friends and my dog, which people say I
2 could not do at this age.
3 If someone asks me if the medicine is
4 working, I say I believe it is because I'm doing
5 stuff I should not be able to do at my age. If you
6 are 100 percent sure that this medicine is not
7 working, don't approve it. But if you're not
8 100 percent sure, then approve this medicine, help
9 other boys who share my struggle. Thank you.
10 (Applause.)
11 DR. ALEXANDER: Thank you. Please hold your
12 applause.
13 MS. VAISH: I am Ana, and Make Duchenne
14 History Coalition arranged for us to be here today.
15 I am Ryan's mother. As he said, he is 13 years and
16 10 months old, and one of the 12 boys getting
17 eteplirsen since 2011. He hasn't missed a single
18 dose and has had no safety issues.
19 When Ryan started the study, he was
20 declining. He walked with lordosis and his toes
21 pointed inwards due to the weakness in his hips,
22 both signs that he would lose ambulation soon.

1 He did not look like a child with Duchenne
2 that you would expect to see walking four years
3 later. However, since 2011, Ryan has maintained
4 the same energy and ability to do day-to-day
5 things, like walk, go to school, play with his
6 friends, go swimming, and shower by himself.
7 We have not given Ryan any more PT or
8 anything other than the recommended care. Before
9 being on the trial, Ryan used to come home from
10 school very tired. Now on eteplirsen, he comes
11 from school and goes straight into the pool. In
12 fact Ryan has been receiving below the recommended
13 dose of steroids.
14 Until March of 2015, he was taking
15 18 milligrams of deflazacort, half of the
16 recommended dose. At that point, Dr. Mendell
17 increased his dose to 24 milligram because it was
18 still very low. That is still below the
19 recommended dose of 33 milligrams according to his
20 weight today.
21 The 0.9 increase in dystrophin may not mean
22 much to the reviewers at FDA, but come, look at the

1 10 boys that are still walking. Come live in the
2 shoes of these children, of my son Ryan, and it is
3 meaningful.
4 Every day that Ryan maintains his ability to
5 walk and live longer matters. Maintaining the
6 ability to do day-to-day things matter. More time
7 matters. More time for our family and hope for
8 even more treatments that will reach your desk soon
9 for approval. The first safe and effective
10 treatment is on your desk today. Please recommend
11 approval of eteplirsen.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker 32 please come to the microphone? Please
15 state your name and any organization you are
16 representing for the record.
17 MS. DWYER WILLIS: My name is Alison Dwyer
18 Willis. I am the mother of Jack and Nolan Willis,
19 patients number 9 and 10 of the original 12 Sarepta
20 clinical trial participants. Before I speak, I
21 think you should hear from them since they are two
22 of the most important voices in the room today.

1 JACK WILLIS: My name is Jack Willis, and I
2 am patient number 9 in the Sarepta trial.
3 NOLAN WILLIS: My name is Nolan Willis, and
4 I am patient number 10 in the Sarepta trial.
5 JACK WILLIS: We have chosen to dedicate the
6 last five years of our lives to this clinical
7 trial, quite willingly. Since we have lost the
8 ability to walk, we have been labeled as the
9 failures of the eteplirsen trial. We come here
10 today not only to show that we are not failures,
11 but to claim victory.
12 NOLAN WILLIS: We claim victory because our
13 lives improved while on drug. Our hearts and lungs
14 performed normally. We had some increase in
15 strength. We noticed when we had to skip a dose we
16 are more tired and lethargic. We know this drug
17 will keep us alive longer.
18 JACK WILLIS: Duchenne patients don't die
19 from not walking, they die from heart and lung
20 failure. We are almost 15 years old with normal
21 function, something which is not necessarily normal
22 for other Duchenne kids our age. We did not have

1 one side effect while we have been on eteplirsen.
2 NOLAN WILLIS: We are not outliers. We have
3 followed the natural progression of Duchenne, which
4 has now changed due to eteplirsen. Even though we
5 stopped walking four years ago, we are still able
6 to pick books off the table, feed ourselves
7 independently, drink without a straw, and brush our
8 teeth without help.
9 JACK WILLIS: We are not failures because we
10 stopped walking. Please stop calling us that.
11 This drug not only preserves the ambulation -- this
12 drug is not only to preserve ambulation, like we
13 said. You don't die from Duchenne by not being
14 able to walk. Maybe had we been on drug sooner, we
15 would still be walking. Why would you make other
16 boys wait when this drug could allow them to walk
17 longer, to feed themselves longer, to hug their
18 parents longer, to live longer?
19 MS. DWYER WILLIS: I was nervous that the
20 boys would not qualify for this trial knowing that
21 Nolan's ambulation was already rapidly declining.
22 Our goal for this trial was not to preserve

1 ambulation. It was to preserve their quality of
2 life and allow them to live longer, period.
3 Nolan took his last steps in February of
4 2012 and Jack joined him in June of that year.
5 They fought hard to stay on their feet as their
6 walking days were really gone before they even
7 started the trial.
8 My boys became known as the kids who were
9 making the data messy, who declined in the 6-minute
10 walk test, who lost ambulation, and everyone began
11 to question if the drug was working.
12 My boys make the data stronger because they
13 are responders, they are making dystrophin. The
14 drug is working in them. The production of
15 dystrophin has changed the trajectory of their
16 disease. My boys regained some upper arm and torso
17 strength, were less fatigued, and regained some of
18 their independence that had been lost.
19 In their case, loss of ability to walk
20 independently has still not preceded a decline in
21 pulmonary function. Thanks to eteplirsen, both of
22 my boys are experiencing a clear deviation from the

1 natural disease course. My sons should give the
2 ad comm panel members confidence that the drug is
3 working in both ambulatory and non-ambulatory boys.
4 Both populations will benefit from the approval of
5 eteplirsen. Thank you.
6 (Applause.)
7 DR. ALEXANDER: Thank you very much. Will
8 speaker 33 please introduce yourself? Please state
9 your name and any organization you are representing
10 for the record.
11 MS. JOHNSON: Our travel was supported by
12 the Make Duchenne History Coalition. My name is
13 Alex Johnson, and I have come here with 42 parents
14 from Britain who have children with Duchenne.
15 We've traveled all this way for 0.9 percent of
16 dystrophin.
17 If eteplirsen gets rightly approved, we
18 would move our family here for 0.9 percent of
19 dystrophin. For those who were disappointed by 0.9
20 of dystrophin or don't know Duchenne well, this may
21 be viewed as an act of desperation. Although the
22 U.S. seems nice enough, we assure you, we would not

1 uproot our entire lives for something trivial.
2 Our decision rests firmly on scientific
3 research. It is well-known in the scientific
4 community that some exon 44 patients have
5 spontaneous exon skipping that results in revertant
6 fibers. This small amount of dystrophin leads to a
7 slower disease progression.
8 Just two days ago, the Bello paper was
9 published revealing that exon 44 patients have a
10 later median loss of ambulation than other
11 deletions on a Kaplan-Meier analysis. Two years
12 more walking is life changing for patients and
13 families.
14 MR. JOHNSON: The FDA calls into question
15 Sarepta's use of a matched natural history control.
16 They claim that the placebo arm of the drisapersen
17 study is a more appropriate control. Most of that
18 data came from European patients.
19 We know there is data from that study for a
20 duration of 2 and a half years, but the FDA has
21 only referenced the first year of data, then looks
22 to other natural history studies on an apparent

1 hunt for a comparator group that appears to
2 diminish eteplirsen's effects.
3 We would like to know when using these
4 untreated cohorts, such as the CINRG data presented
5 today as a comparator, did the agency apply the
6 appropriate filters, such as age greater than 7 and
7 baseline 6-minute walk score, to ensure the closest
8 possible apples to apples comparison.
9 MS. JOHNSON: We know that being in a trial
10 can incentivize functional improvement. Maybe at
11 first, these boys on this study were influenced by
12 what the briefing document describes as expectation
13 bias, motivation, and coaching. Maybe.
14 But this is Duchenne we're talking about,
15 and we want the panel to know that every parent
16 motivates their child to keep walking. Every
17 parent loses that fight. Every parent, except
18 those of the 10 out of 12 boys on this study; yes,
19 they were motivated, but motivation alone cannot
20 account [mic off].
21 (Applause.)
22 DR. ALEXANDER: Thank you very much. Will

1 speaker 34 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.
4 MS. FURLONG: My name is Pat Furlong, and I
5 am president and CEO of Parent Project Muscular
6 Dystrophy. I have nothing financial to disclose.
7 On Friday, April 29th, my son Patrick died.
8 He was just 15. He was Billy Ellsworth's age. He
9 stopped walking at 9, and at the time of his death,
10 he couldn't lift his hand to his mouth.
11 I spent those last nights with him
12 attempting to remove secretions from pneumonia. It
13 felt like I was suctioning concrete through a
14 straw. Patrick was tired, and he tried to smile,
15 but we knew it was goodbye.
16 Like my son Christopher, who died 7 months
17 earlier on September 29th, Patrick had no options.
18 None. Christopher and Patrick followed the
19 predicted natural history. They were off their
20 feet at 10 years old, and they died in their teens.
21 Today we're talking about a drug with
22 significant great impact, one that is focused on

1 the fundamental defect in Duchenne, restoring
2 dystrophin. Eteplirsen is safe. Four years of
3 safety data with no adverse effects, no SAEs, none
4 whatsoever. We can argue small numbers. We can
5 argue about the quantification of dystrophin.
6 What is critical to discuss is the impact of
7 an incremental effect. A positive incremental
8 effect has a ripple effect across a lifetime.
9 Extending ambulation, preventing scoliosis,
10 delaying the need for ventilation, improving family
11 stability, decreasing the financial impact in terms
12 of accommodation, school, home, employment, and
13 most of all, improving and preserving the quality
14 of life.
15 We've done a benefit-risk study about
16 incremental benefit. The overwhelming priority of
17 the parents that participated was slowing disease
18 progression. These are important milestones,
19 measures of intermediate endpoints that should
20 serve as a future reference point for all
21 regulators and developers.
22 Your goal, the FDA, is to improve how an

1 individual feels, functions, and survives. If you
2 ask these boys, I think they would say absolutely
3 to that. So that's going to require considerable
4 flexibility for all rare disease assessments.
5 Congress agreed and provided tools such as
6 accelerated approval. In addition, they told you
7 to listen to the patient voice. Inclusion of the
8 patient in decision making and those choices will
9 be best be heard via the more creative approaches
10 to rare disease development, which better capture
11 patient centered outcomes.
12 Patient-focused tools are of limited value
13 if we continue to operate in a rigid and
14 adversarial manner. Today, I'm asking for a
15 paradigm shift for all parties, FDA and industry,
16 to commit themselves to a fundamentally
17 collaborative approach, both in this eteplirsen
18 decision and in hopefully the many future INDs and
19 DNAs that come before you. I urge the committee to
20 exercise maximal flexibility. [mic off].
21 (Applause.)
22 DR. ALEXANDER: Thank you very much. Will

1 speaker 35 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record. Once again, please hold your
4 applause until all speakers have finished.
5 MS. KELLY: My name is Melanie Kelly, and I
6 have two sons with Duchenne muscular dystrophy,
7 Jacob and Liam.
8 MR. KELLY: My name is John Kelly. I'm
9 Melanie's husband.
10 MS. STELLY: My name is Trina Stelly. I
11 have one son who is 12 with Duchenne, and I have an
12 8-year-old daughter who is a manifesting carrier.
13 MS. PEASE: My name is Katherine Pease. I
14 have one son 8 years old with Duchenne muscular
15 dystrophy.
16 MR. DENGER: My name is Brian Denger. Our
17 group represents those who are amenable in this
18 therapy and relive the agony of missing the
19 threshold for inclusion in this clinical trial. We
20 are living the history of Duchenne muscular
21 dystrophy.
22 We read in the briefing documents how FDA is

1 not impressed by the slowed progress of the
2 eteplirsen patients because boys with Duchenne can
3 lose ambulation between ages 8 and 18. We are
4 concerned the reviewers are confusing something
5 that is possible with something that is common.
6 Are there outliers who are walking at 18? Yes. Is
7 it common? No.
8 I have two sons affected by Duchenne.
9 Matthew stopped walking at 8. His was a steady
10 decline in physical ability leaving him unable to
11 perform activities of daily living by 12. He
12 succumbed to heart failure at 20.
13 His brother, Patrick, who is now 21, stopped
14 walking at age 13. Though he walked longer, his
15 progression followed the same path as his brother,
16 just several years later.
17 We long came to appreciate that preserving
18 function would be important and a life changing
19 breakthrough. The difference in being able to walk
20 longer, Patrick did at age 13, meant he didn't need
21 spinal fusion surgery, unlike his brother who
22 stopped walking at 8 and needed surgery at 13.

1 The level of ability of participants in
2 Sarepta's trial exhibit is far different than what
3 any of our sons experienced. Walking independently
4 at 14, 15 is not the norm for someone who has
5 Duchenne. These patients are walking well.
6 If you witnessed the last months of walking
7 for someone with Duchenne, you'd realize how
8 starkly different this truly is. In the final year
9 of walking, not only do patients tire and have a
10 significantly slower pace, but they fall, and they
11 fall hard regularly.
12 Nearing the end, they need someone to help
13 them stand, hold them upright while they find their
14 balance, only to walk a meter or 2, not 6 minutes,
15 before collapsing into a heap and wait to be picked
16 up. No amount of motivation stops that tree from
17 falling. That's not the same experience we see for
18 the boys in the study. They walk with more balance
19 and confidence.
20 We represent the patients who are amenable
21 to this drug, and not one of our boys walked past
22 the age of 13. As a parent who has lost a son to

1 Duchenne, I don't need a reminder of how time
2 passes so quickly. We wait and watch as function
3 is lost never to be regained. Each of us asks, how
4 much longer. Thank you.
5 (Applause.)
6 DR. ALEXANDER: Thank you very much. Will
7 speaker 36 please introduce yourself. Please state
8 your name and any organization you are representing
9 for the record.
10 DR. NELSON: My name is Stanley Nelson. I'm
11 a professor of human genetics and co-director of
12 the Center for Duchenne Muscular Dystrophy at UCLA,
13 and I have no financial interest in the outcome of
14 the meeting today. I care for children with
15 Duchenne and am an expert in genetic and genetic
16 modifiers. I've served on clinical trials, data
17 monitoring committees, and advisory boards related
18 to Duchenne.
19 DuchenneConnect is the largest online
20 registry, and in 2014, my group published a
21 multivariate analysis looking at all 78 parameters
22 collected and identified that the most strong

1 correlate with age at loss of ambulation was by far
2 the use of steroids. This is using a hard endpoint
3 of age at loss of ambulation. There was a minor
4 difference between daily deflazacort usage and
5 daily prednisone.
6 I'll also comment that the effect of LTBP4,
7 which was brought up by Glen Nuckolls on the
8 advisory committee, would be of minor concern in
9 comparing these sample sets, partly because the
10 LTBP4 allele, the haplotype, seen in a homozygous
11 state would only be present in about 10 percent,
12 and the effect of LTBP4 observed in three
13 independent studies is much smaller than the effect
14 observed by steroids, so controlling for steroids
15 is most important.
16 I can also give you a little bit of a
17 personal take in terms of the hard point of loss of
18 ambulation. I'm also here as the father of Dillon,
19 age 15, living with Duchenne. He lost his ability
20 to walk at age 13 and a half. Most boys that I
21 know socially, and Dillon in particular, are very
22 resistant to this transition and fight hard to push

1 it back as long as possible.
2 This is the case for Dillon and makes age at
3 loss of ambulation actually a rather hard endpoint.
4 You can change it by weeks, maybe months; extending
5 it longer is actually very difficult to do. It
6 makes it also an irreversible and highly
7 undesirable endpoint with substantial consequences
8 to his environment and care needs.
9 I know this well, and this point has been
10 brought up by several in the open public hearing
11 and in the Sarepta presentation, that Dillon lost
12 ambulation at 13 and a half and is therefore on the
13 slightly more mild end of Duchenne, and that's
14 supported by multiple natural history data. And
15 yet, when he was 9, his 6-minute walk distance, as
16 determined by being in a different clinical trial,
17 would have compelled him not to be a part of this
18 clinical trial.
19 So the boys that are at the outlier end,
20 those boys that are still walking at age 14, 15,
21 16, also tend to have better physical measurements
22 at ages 7, 8, 9 and 10, the exact group that

1 Sarepta was hoping to exclude from this.
2 I'll also note that many of these opinions
3 were shared in a letter drafted by 36 experts in
4 Duchenne that actually do support that there is
5 substantial evidence of efficacy for eteplirsen
6 based on the clinical data and based on the
7 reasonable comparison to multiple external
8 data sets. Thank you.
9 (Applause.)
10 DR. ALEXANDER: Thank you very much. Will
11 speaker 37 please introduce yourself? Please state
12 your name and any organization you are representing
13 for the record.
14 MR. PROCKO: We are Bill and Kim Procko, and
15 thank you to CureDuchenne for our travel and
16 lodging arrangements. Our son, Evan, is one of the
17 original 12 participants. During the course of
18 this trial, we have observed profoundly positive
19 changes to his physical condition, each one of them
20 contradicting normal Duchenne disease progression.
21 Here is what 0.9 percent can do.
22 Natural history suggests that once a boy

1 with Duchenne loses the ability to get up off the
2 floor, he will also lose the ability to walk within
3 the next 12 to 24 months. Evan remains walking
4 3 years and 2 months after losing this ability.
5 Prior to eteplirsen, Evan slept fitfully
6 through the night, his fists clenched so tightly we
7 could hardly pry his fingers open, his calves in
8 full contracture. After eteplirsen, Evan's sleep
9 became relaxed, his palms open, calves soft,
10 without contracture. Evan's body now rests and
11 recovers at night as it should.
12 Prior to eteplirsen, Evan fell 2 to 3 times
13 per week. During the course of this trial, Evan's
14 fall frequency has reduced to 1 fall every 2 to
15 3 weeks. The amount of Evan's daily walking has
16 remained nearly the same.
17 Prior to eteplirsen, Evan's digestive
18 process was noticeably slower than it is today,
19 with bowel movements 3 to 4 days apart requiring
20 laxatives. At present, bowel movements occur daily
21 without aid. His diet has always been healthy.
22 The only change has been eteplirsen.

1 On September 6, 2015, Evan suffered a spiral
2 fracture to his right tibia. We knew that a broken
3 leg and subsequent muscle atrophy from weeks in a
4 cast for a 12-year-old with Duchenne more often
5 than now spells the permanent end of ambulation.
6 For Evan, however, after 7 weeks in a cast and
7 boot, he stood up and walked unassisted.
8 According to his UF Schanz orthopedic staff,
9 recovery time was indistinguishable from any non-
10 Duchenne patient, and on November 2nd, only 8 weeks
11 after his fracture, Evan was back in Ohio
12 performing two successful 6-minute walk tests for
13 Sarepta.
14 These observations contradict Duchenne
15 progression. In the last four years, we've done
16 nothing out of the ordinary concerning protocol
17 with Evan's care except for eteplirsen. The FDA's
18 January briefing documents stated that the boys in
19 our study have received intensive physical therapy.
20 The date of Evan's last physical therapy
21 appointment was May 13, 2009. At home, we do a set
22 of stretches 4 to 5 times per week. If anything,

1 this falls below recommended PT regimen.
2 MS. PROCKO: The benefits we have presented
3 from 0.9 percent dystrophin are significant to us.
4 Now, I wonder how many more years does that
5 0.9 percent give Evan independence to pour more hot
6 sauce on his burrito or to wrap his arms around me
7 in a hug.
8 Duchenne has taken away Evan's dystrophin.
9 Eteplirsen has given him some back. Now, it's in
10 your hands to allow him to keep it or take it away
11 from him again.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker 38 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.
17 MS. PENROD: My name is Marissa Penrod, and
18 my son Joseph has Duchenne. My son and the sons of
19 the parents standing with me here right now are
20 waiting for a treatment. This was a significant
21 year for Joseph. It was the year that Duchenne
22 stole Joseph's ability to walk. I assure you, he

1 had no choice. He wanted desperately to keep
2 walking. It was not a question of motivation or
3 mindset. Joseph lost ambulation because he has
4 Duchenne.
5 We tend to think of loss of ambulation as
6 the end of something, the end of walking, but
7 really it's just a new beginning. It's the
8 beginning of a new kind of decline. Decline in
9 Duchenne comes in many forms. Dave and Maria's son
10 Ryan, and Kelly's son Jack, demonstrate the immense
11 burden of Duchenne through their struggle with
12 self-image.
13 Anessa's teenage son, Tyler, can no longer
14 go to his friend's house because they're not
15 accessible. Natalie's son, Max, can no longer move
16 his arms to scratch his own face. And Kat's [ph]
17 son, Dusty, has just 12 percent of his lung
18 function remaining. He is literally on his last
19 breaths.
20 I know that Joseph's arm strength will go
21 next. He won't be able to feed himself. I will
22 have to hold a book for him to read, and hugs will

1 be a memory. We will face scoliosis, spinal
2 surgery, pulmonary distress, heart failure. The
3 loss of ambulation matters, but what matters more
4 than losing ambulation is maintaining ambulation.
5 Thanks goodness for eteplirsen. Today
6 should not be a day for uncertainty or fear, it
7 should be a day of celebration. We know that many
8 clinical trials and potential treatments comes with
9 risk. Not this one. We know that some decisions
10 you have to make are clouded by uncertain clinical
11 benefits. Not this one.
12 Today we should celebrate and honor the
13 truth, and we must not be distracted from that
14 truth. Four years later, 4 biopsies later, that
15 surgery under general anesthesia, they're still
16 walking. How much more will you ask of them? When
17 will their sacrifice be enough?
18 The FDA gave guidance to Sarepta in April of
19 2014 urging them to identify matched natural
20 history cohorts. You can't move the target now, it
21 is too late and our sons deserve better. Our kids
22 are not your science experiment. They're not a

1 sample or a cohort or a subject. They're someone's
2 brother and son, someone's grandson, and student,
3 and best friend. Our children are not here to
4 serve the science, but the science must always
5 serve our children, and eteplirsen does that.
6 If not you to acknowledge the evidence that
7 eteplirsen works, if you not honor the tools give
8 to you by Congress and FDASIA to demonstrate
9 flexibility, then who will? It's time to stop
10 talking about flexibility and to show us. We don't
11 hope you do the right thing, we expect you to do
12 the right thing, and the right thing is to say yes.
13 (Applause.)
14 DR. ALEXANDER: Thank you very much. Will
15 speaker 39 please introduce yourself? Please state
16 your name and any organization you are representing
17 for the record.
18 DR. JUHASZ: Hello. My name is Rose Juhasz,
19 from the University of Michigan Medical School,
20 support by Make Duchenne History. My son is in the
21 confirmatory study control arm amenable to exon 53
22 skipping. My comments today are coming both as a

1 parent and as an academic colleague who has worked
2 for nearly 15 years in the study and support of
3 personalized medicine. I currently manage a
4 $13 million NCI research program on precision
5 medicine in early stage breast cancer.
6 I could stress that precision medicine is
7 also here to treat children, and that we do so by
8 skipping exons. Instead, I refer you to a recent
9 JAMA neurology viewpoint by noted clinician
10 scientist Eva Feldman. She concluded, and I quote,
11 "Exon skipping offers tremendous promise, and the
12 impact on Duchenne patients may alter the practice
13 of neuromuscular medicine by bringing personalized
14 genetic therapies."
15 I could praise the FDA's accelerated
16 approval paths for select treatments in early stage
17 breast cancer. It's helped to render that disease
18 highly survivable and rich with treatments. We
19 desire similar flexibility for just a first
20 treatment in Duchenne. Without it, this is
21 disparity, and our children deserve better.
22 As today is about children, I'll share on a

1 clinical cohort I find relevant. Completing my own
2 doctoral work, I had the privilege to study some of
3 the first deaf kids to receive cochlear implants.
4 They were implanted at relatively old ages after
5 prolonged auditory depravation. The FDA did not
6 initially favor implanting kids earlier despite
7 known critical periods for speech and language and
8 preserving auditory function.
9 Positive outcomes in those first kids were
10 not immediate. Those who did respond needed years
11 of device use. For others, it was too late to get
12 full benefit from a technology now known as
13 groundbreaking.
14 Those were children failed by the FDA
15 process. The technology was there for years;
16 access was delayed. These are kids who will then
17 live out the rest of their lives knowing that the
18 quality of life could have been quite different had
19 it not been for regulatory disparities and delays
20 for children. Despite those odds and having
21 received the first devices, there were some stand
22 out responders. They became known in our research

1 group as the stars.
2 Today you have met the stars of exon
3 skipping. They have walked up here and stood and
4 told you that this drug is working and important
5 for them. And as I stand here 15 years later,
6 please hear this message.
7 No child should have waited then for the
8 chance to hear, and no child today should be
9 waiting this long to keep walking or to continue to
10 use his limbs. This is a fatal disease. We cannot
11 afford to fail them. Thank you.
12 (Applause.)
13 DR. ALEXANDER: Thank you very much. Will
14 speaker 40 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.
17 DR. SHIEH: Good afternoon. Yes, my name is
18 Dr. Perry Shieh, and I'm an associate professor of
19 neurology at UCLA, where I serve as the clinic
20 director of the muscular dystrophy clinic. I would
21 like to ask if somebody could pull up the slides
22 for speaker number 36.

1 It's through this clinic that I currently
2 care for approximately 100 boys and men with
3 Duchenne muscular dystrophy.
4 DR. ALEXANDER: I'm sorry, we're unable to
5 provide those slides at this time.
6 DR. SHIEH: Okay. That's fine. And I'm
7 also an investigator in numerous clinical trials
8 for Duchenne muscular dystrophy, including three
9 ongoing clinical trials involving eteplirsen. I
10 think the most important question today is whether
11 eteplirsen works. Is whether eteplirsen clinically
12 improves Duchenne muscular dystrophy patients. And
13 I do like to thank the FDA for their caution and
14 their extensive discussion about the potential
15 shortcomings of the study data.
16 Nonetheless, I would like to emphasize that
17 the study data do show reasonable substantial
18 evidence of efficacy. I would like to echo the
19 opinions of my colleagues before me that loss of
20 ambulation is truly a hard endpoint. It is not
21 something that is optional.
22 Generally, people who are not able to do

1 6-minute walk test will not be able to do anything
2 very soon. And looking at the study data, looking
3 at loss of ambulation as a function of a drug
4 exposure seems to be the most appropriate way to
5 analyze the data because baseline characteristics
6 and baseline 6-minute walk tests do predict the
7 future outcome, the future course of these boys.
8 Now, one may argue that the 4-year data was
9 not blinded. It was not a placebo-controlled
10 study. However, this is an issue of perhaps
11 placebo effect, and many publications have
12 indicated in the past that placebo effect is
13 generally small, temporary, and relatively
14 subjective.
15 The placebo effect would not prevent
16 Duchenne boys, based on a hard endpoint such as
17 loss of ambulation, from losing ambulation.
18 Placebo effect cannot prevent them from losing the
19 ability to walk. In fact, I believe it is the
20 collection of study data over four years of this
21 very progressive disease that makes this data very
22 convincing and robust, and it would not be possible

1 to perform the double-blind placebo-controlled
2 study over the same amount of time.
3 So although 12 patients may seem like a
4 relatively small number for a clinical trial, the
5 effect observed is still impressive. Of course, we
6 would like the sponsor to complete the confirmatory
7 studies that are already ongoing that will have
8 many more patients, but the data have presented so
9 far are persuasive, and additional safety data from
10 ongoing studies, I do not believe that there's any
11 reason to limit access to this medication.
12 In other words, I would like to be able to
13 prescribe this medication to other Duchenne boys
14 who are amenable exon 51 skipping. The risk of
15 harm appears to be minimal. And with close
16 monitoring, I believe this is the best way to
17 acquire additional information about this effective
18 treatment. Thank you.
19 (Applause.)
20 DR. ALEXANDER: Thank you very much. Will
21 speaker 41 please introduce yourself? Please state
22 your name and any organization you are representing

1 for the record.
2 DR. MCNALLY: Thank you. My name is
3 Elizabeth McNally. I am a physician and scientist.
4 I direct the Center for Genetic Medicine at
5 Northwestern University in Chicago. I'm also a
6 cardiologist who specializes in providing care for
7 those with neuromuscular disease.
8 I'm a physician in the Muscular Dystrophy
9 Association Clinic at Northwestern Medicine, where
10 I work closely with neurology and pulmonary experts
11 caring for those with advanced Duchenne muscular
12 dystrophy. I have no consulting relationship with
13 Sarepta. I have no bias in looking at the data
14 here today.
15 Boys with DMD grow to be men with DMD, and
16 they should not be forgotten here today in this
17 discussion. There's been much focus and emphasis
18 on walking as an endpoint in DMD, but walking is an
19 not an endpoint for a young man with DMD.
20 Retaining upper limb strength is important
21 for being able to eat, drive a wheelchair, type on
22 a keyboard, and hold a job. These are the

1 endpoints that matter. Walking is a surrogate for
2 what happens to many muscles in DMD.
3 We know well from the earliest genetic DMD
4 studies that the amount and quality of dystrophin
5 production is the primary determinant of outcome in
6 this disease. Dystrophin production linearly
7 correlates with outcome. There has never been
8 shown to be a threshold effect under which
9 dystrophin level does not matter. Any increase in
10 dystrophin is meaningful.
11 The goal of exon skipping is to convert the
12 more severe form of disease, DMD, to the milder
13 form of disease, Becker muscular dystrophy, but
14 what does that really mean?
15 I think of the many DMD guys I take care of.
16 I think of Ryan and I think of Joe in particular.
17 They have DMD. They went to college, they
18 graduated, but it was hard to find work with the
19 fact that they had lost so much upper limb
20 strength, and post-college life has been hard for
21 them. With even modest improvement in upper arm
22 strength, they would be able to do so much more.

1 I am also a scientist and an established
2 investigator in the neuromuscular field for more
3 than 20 years. As a scientist, the FDA conclusions
4 regarding dystrophin quantitation presentation are
5 most puzzling. We heard that three independent
6 veterinary pathologists arrived at different
7 quantitative values than the pathologist from
8 Nationwide Children's Hospital, and based on this
9 discrepancy, the immunofluorescence results were
10 devalued.
11 The dismissal of the immunofluorescence data
12 seems to be skipping the critical point that these
13 veterinary pathologists identified a clear
14 difference between treated and untreated patients,
15 17 percent versus less than 1 percent.
16 It is implied that immunoblotting is somehow
17 superior to immunofluorescence microscopy, and this
18 is plainly inaccurate. Blotting methods are
19 hampered by the large size of dystrophin, its high
20 susceptibility to proteolysis, and the challenges
21 in extracting dystrophin adequately from fibrotic
22 muscle.

1 Blotting fails to take into account for the
2 regional distribution of dystrophin expression
3 within a muscle. To be fair and unbiased, both
4 blotting and fluorescence methods should be
5 considered together.
6 Today, we saw data that eteplirsen treated
7 boys walk longer, walk farther, have more
8 dystrophin on blotting, and on fluorescence.
9 Moreover, this drug is safe. It seems prudent to
10 recommend accelerated approval based on the data.
11 (Applause.)
12 DR. ALEXANDER: Thank you. Will speakers
13 number 42 introduce yourselves? Please state your
14 name and any organization you are representing for
15 the record.
16 MR. MARQUEZ: My name is Ethan Marquez. I
17 am joined by Kadee Roden, Christina Burrell, and
18 Sandra Katzin. Each one of us has a son with
19 Duchenne muscular dystrophy and enrolled in the
20 confirmatory trial of eteplirsen.
21 Our boys are between the age of 10 and
22 13 years old and have been taking eteplirsen for

1 approximately one year. We all have noticed our
2 boys doing things they weren't able to do before
3 the trial, and I'm here to share our stories.
4 Before eteplirsen, Sandra's son, Ethan, was
5 extremely lethargic, unable to walk for long
6 distances. Today, he can walk alongside his mother
7 without getting exhausted. His stride is more
8 stable. He does not fall as much as he used to.
9 This is important to note because a
10 reduction of Duchenne falls is a commonly reported
11 result of eteplirsen. This is a massive quality of
12 life improvement because it means he is less likely
13 to fall and injure himself.
14 Christina's son, Xavier, and Kadee's son,
15 Morgan, have also experienced an increase in
16 strength since being on eteplirsen. Since starting
17 the trial, they have the ability to keep up with
18 their friends at school and not come home
19 exhausted. Xavier can independently dress himself,
20 comb his hair, put on his shoes.
21 DR. ALEXANDER: I'm sorry for interrupting.
22 If you're having conversations, can you please have

1 those outside.

2 MR. MARQUEZ: Tie his shoes, and even brush

3 his teeth. These are daily tasks that he could not

4 do before eteplirsen. Since my son, Peyton,

5 started on eteplirsen over a year ago, my wife and

6 I have seen him stabilize, gain his strength, and

7 even move in ways he has never done before. This

8 has not happened to a boy with Duchenne. We've all

9 seen eteplirsen working.

10 Before starting the trial, Peyton could not

11 kick his foot above the air, now he can kick his

12 foot above his waist.

13 (Laughter.)

14 MR. MARQUEZ: Before eteplirsen, he was

15 unable to pull himself out of our pool. He would

16 just barely hang onto the edge. Now he can pull

17 himself out. He used to struggle to climb into our

18 SUV and onto his bed, now he can do both with ease.

19 Before he came home exhausted and needed a nap.

20 Now he has the stamina to participate all day in

21 school and after school activities, and even stay

22 awake until bedtime.

1 Eteplirsen has given us hope for his future.
2 We no longer plan his funeral. Now, when Peyton
3 talks about driving, attending college and becoming
4 a scientist, because of eteplirsen, we believe it's
5 possible.
6 I implore you, recommend this drug. It is
7 clear to us, our sons, our children's teachers,
8 family and friends that eteplirsen works. It is
9 safe and needs approval so many of the boys have a
10 chance. We already know the results without
11 eteplirsen.
12 This committee has the ability to recommend
13 that the FDA approve a drug that will improve the
14 quality of life for our entire community. It will
15 lead to other breakthroughs. To not approve it for
16 many other boys that are suffering, that have
17 suffered, and that will suffer in the future is not
18 only confusing but outright cruel. Substantial
19 evidence of the effectiveness of eteplirsen is
20 clear. Thank you.
21 (Applause.)
22 DR. ALEXANDER: Thank you very much. Will

1 speaker 43 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.
4 DR. CHAMBERLAIN: My name is Jeff
5 Chamberlain, and I'm a professor of neurology at
6 the University of Washington. I'm also director of
7 the Senator Paul D. Wellstone Muscular Dystrophy
8 Research Center, and I'm a paid member of the
9 Sarepta scientific advisory board.
10 I've been studying the molecular genetics of
11 DMD for 30 years with a focus on dystrophin
12 expression and the development of gene therapy.
13 For these goals, my lab has developed transgenic
14 mice, we've developed adenoviral vectors,
15 lentiviral vectors, and AAV vectors in order to
16 study how much dystrophin is needed to prevent or
17 to reverse the pathophysiology of DMD.
18 We've also been looking at the relative
19 effects of producing full length Becker-like and
20 micro dystrophin proteins in muscle. These studies
21 have been remarkably consistent in showing that
22 very low levels of dystrophin can have significant

1 effects on muscle function.
2 Now, it was mentioned earlier that
3 dystrophin levels as low as 10 percent of normal
4 can prevent and largely reverse the dystrophic
5 pathology, and our data and animal models certainly
6 agrees with that. However, those levels are
7 essentially what are needed for a cure, and we're
8 not here today talking about a curative therapy.
9 It's very important to emphasize that our
10 studies of animal models also showed that much
11 lower levels of dystrophin have a clear and
12 measurable impact on muscle function, and this is
13 true whether we're expressing full length
14 dystrophin, Becker-like dystrophins, or even the
15 micro dystrophins that were developed in my
16 laboratory.
17 Our studies of dystrophin function have also
18 demonstrated a mechanical role mediating the
19 lateral transmission of force from within a
20 myofiber into the extracellular matrix. And the
21 consequence of this is that a single dystrophin
22 positive myofiber has a clear protective effect on

1 adjacent dystrophin negative myofibers.
2 Thus, the overall protection that's
3 conferred by low dystrophin expression is greater
4 than what you would predict by a simple comparison
5 to normal dystrophin levels, and it's greater than
6 you would see just by looking at the percent of
7 dystrophin positive fibers. We have clear data
8 that even a single dystrophin positive fiber
9 protects adjacent fibers, so patchy or mosaic
10 expression of dystrophin has a wider effect than
11 just counting dystrophin positive fibers. In fact,
12 our studies indicate that any dystrophin expression
13 has a beneficial effect on overall muscle function
14 and physiology.
15 In summary, our data in animal models
16 acquired through a variety of different methods
17 predict that the dystrophin expression patterns
18 that have been observed with eteplirsen are
19 sufficient to achieve a significant increase in
20 muscle function. Thank you.
21 (Applause.)
22 DR. ALEXANDER: Thank you very much.

1 Because we're running over, I'd like to take a
2 break now. So we'll take the afternoon break at
3 this time. So this is going to substitute for the
4 break that would be coming up at the end of the
5 open public hearing. So we'll take a 15-minute
6 break at this time. Thus, we'll come back at 10
7 minutes after 5, 5:10.
8 Panel members, please remember that there
9 should be no discussion of the meeting topic during
10 the break amongst yourselves or with any member of
11 the audience. Once again, we'll resume at 5:10.
12 (Whereupon, at 4:55 p.m., a recess was
13 taken.)
14 DR. ALEXANDER: If you can please take your
15 seats. We're going to be beginning in just a
16 minute with open public hearing speaker number 44
17 in just a minute.
18 (Pause.)
19 DR. ALEXANDER: Okay. Out of respect for
20 those public speakers, if you are still conversing
21 and wish to continue, please do so in the hallways.
22 And we'll be beginning now where we left off which

1 is with speaker number 44.
2 If speaker number 44 could introduce
3 yourself, please state your name or any
4 organization you are representing for the record.
5 MR. WOLF: We appreciate the break, but you
6 can't ice this kicker so thank you.
7 I'm Brian Wolf, and I am joined by exon 45
8 and 53 waiting group, and our travels was arranged
9 by the Make Duchenne History Coalition.
10 Our group consists of Amy Aikens,
11 Chris Daimler and Cindy Quitzau. We represent
12 Duchenne patients in need of access to follow-on
13 drugs, specifically exon skipping 45 and 53, and we
14 fully support the approval of eteplirsen.
15 We are here to support our Duchenne
16 community for exon skipping 51 and believe that
17 future exon skipping drugs will advance with the
18 approval of this first drug. While we wait, our
19 sons continue to get weaker and we are running out
20 of time.
21 Four and a half years ago, we began to hear
22 and see the stories of continued ambulation and

1 increased flexibility and zero side effects in the
2 patients in the eteplirsen 201/202 trial aside from
3 their encouragement. We also see the publicly
4 released data and were encouraged by eteplirsen's
5 unprecedented results. We need to include the rest
6 of our Duchenne family in this huge vehicle of
7 hope.
8 The approval of eteplirsen would be our
9 first critical step in getting this new life-saving
10 technology in the hands of other Duchenne patients,
11 including our sons. The FDA has the authority to
12 approve this drug next month and make a meaningful
13 difference in the lives of families.
14 As parents, we have become advocates,
15 speakers, caregivers, educators, and fighters, and
16 we have passed those traits to our sons and
17 daughters, those with Duchenne and those without.
18 Despite how the media sometimes portrays us, we are
19 not desperate parents. We are educated in the
20 data, the expert scientists and clinicians support
21 us, and we are not willing to give our children a
22 drug that isn't safe or doesn't work.

1 The FDA in this division have wavered with
2 their guidance far too many times, which in turn
3 has delayed the opportunity for our sons to receive
4 the needed exon skipping drug. Today, you have
5 renewed opportunity to follow FDASIA and use the
6 tools Congress has provided FDA to expedite access
7 of life-saving treatments to patients who need
8 them.
9 Today, we ask the committee to consider the
10 total and quality of eteplirsen's data and the
11 patient and expert testimony and please, recommend
12 eteplirsen for accelerated approval.
13 Our community has already experienced many
14 unnecessary delays related to this drug. Do not
15 waste any additional time so that thousands of
16 other waiting Duchenne patients from our group that
17 we represent can make Duchenne history by outliving
18 their diagnosis. Thank you.
19 DR. ALEXANDER: Thank you very much.
20 (Applause.)
21 Will speaker number 45 please come to the
22 podium and introduce yourself? Please state your

1 name and any organization you are representing for
2 the record.
3 MR. KUNKEL: Yes. My name is Lou Kunkel
4 from Boston Children's Hospital in Boston, in the
5 Department of Genetics and Pediatrics at Harvard
6 Medical School. I am a paid member of Sarepta's
7 scientific advisory board, and my travel here was
8 paid for by Make Duchenne History Consortium.
9 My laboratory was the laboratory which
10 identified the gene responsible for Duchenne
11 dystrophy back in 1986. In 1987, we described the
12 encoded protein, dystrophin, and we showed that
13 major mutations at this two-and-a-half megabase
14 locus were deletions in both the severe Duchenne
15 form of dystrophy, as well as the milder form of
16 Becker muscular dystrophy.
17 We proposed, at the time, that the
18 difference between deletions in Duchenne patients
19 and Becker patients were based on the effect they
20 had on the translational reading frame of the
21 encoded protein. We predicted Duchenne patients
22 would make no protein because they would have

1 premature stop because they've disturbed the
2 reading frame, whereas Becker patients would have
3 an internally truncated protein but that it would
4 be made.
5 We showed, in 1988, that protein was not
6 being made in Duchenne biopsies, published in the
7 New England Journal of Medicine. And in that
8 article, we talked about the limit of our
9 detection. This is in 1988, and this is where this
10 3 percent number comes from.
11 Eric Hoffman used both myocin staining
12 post-transfer to estimate underloaded gels and said
13 that he couldn't probably see below 3 percent. But
14 that's a long time ago, and the technology has
15 changed a lot since then. Becker patients were
16 shown to make an abnormal truncated protein of
17 variable degrees of levels of the protein.
18 This led us to propose, as Steve Wilton did,
19 that, potentially, we should try to block the
20 inclusion of exons and convert a Duchenne into a
21 Becker by interchanging the reading frame and
22 producing protein.

1 Sarepta's eteplirsen is designed to block
2 exon 51 in 13 percent of dystrophin deletion
3 patients. They documented that exon skipping 51 is
4 skipped based on RTPCR, so the mechanism of action
5 of that drug is working. They document on
6 immunofluorescence that the protein is being made,
7 albeit at not quantifiable levels but way above
8 what we've ever seen for revertant fibers.
9 But for me, the best evidence was their
10 Western blots, which showed 0.9 percent. We never
11 see 0.9 percent in patient biopsy samples, and so
12 this is really an appreciable amount. Consistent
13 with this was the clinical progression. These make
14 dystrophin, its safe, and I believe there's no
15 reason not to approve.
16 (Applause.)
17 DR. ALEXANDER: Thank you very much. Will
18 speaker number 47, please come to the podium and
19 introduce yourself?
20 MS. LEFFLER: I'm 46.
21 DR. ALEXANDER: I'm sorry, 46. Will speaker
22 46, please introduce yourself? Thank you. Please

1 state your name and any organization you are
2 representing for the record.
3 MS. LEFFLER: My name is Mindy Leffler, and
4 I'm here representing my family. We are listening
5 to two versions of reality today: Sarepta's is
6 that a group of boys who are on the cusp of
7 decline, took an experimental drug, and progressed
8 slower than expected. The FDA's is a group of boys
9 with DMD who frequently walked past the age of 13.
10 Sarepta lucked into a group of them, and everything
11 else you're hearing today in support of efficacy is
12 either wishful thinking or coincidence.
13 Here is my son's story, and you can decide
14 which it supports. Aiden screened for the study
15 we're evaluating today. He walked too far to fit
16 the inclusion criteria and he was not included. We
17 went with plan B, which ended up being the placebo
18 arm for driaspersen, the very data set cited in FDA
19 briefing documents as the most accurate control for
20 eteplirsen.
21 So he was too functional for the eteplirsen
22 study, and yet somehow he's the perfect control for

1 it.

2 When Aiden was on driaspersen, I relied on

3 casual observation to draw my conclusions. By the

4 time he was off drug, I had nothing definitive to

5 say. So at age 11, when Aiden was put on

6 eteplirsen, I was not going to rely on observation.

7 I wanted to be objective about how he was doing

8 because I didn't want him spending any more time on

9 a drug that might not work.

10 I picked the things he struggled with the

11 most: getting off the floor, going upstairs,

12 getting in a car, and spontaneous collapsing. I

13 took a video at regular intervals and I kept a

14 daily log of collapses.

15 So I am not standing up here with anecdotes

16 about how strong my son was on drug and simply

17 asking you to trust me. I'm saying that I put

18 together a perspective PRO program on Aiden when he

19 started eteplirsen, and I captured data regularly

20 in a rigorous way.

21 On eteplirsen, Aiden went from collapsing

22 2 to 5 times per day to not collapsing anymore, at

1 all. On eteplirsen, Aiden regained the ability to
2 pull himself into the car independently for the
3 first time in over a year. As of this morning, he
4 can still do it. I would challenge anyone to find
5 that kind of progression, regaining definitively
6 lost milestones anywhere in the natural history of
7 Duchenne.
8 The briefing documents spend a great deal of
9 time criticizing each piece of data independently,
10 but if you look at the data as a whole, either
11 eteplirsen works or there are a whole lot of
12 coincidences pointing in the same direction.
13 Medical students are often told when they
14 hoof beats to think of horses, not zebras; look to
15 the obvious conclusion rather than searching for
16 the unlikely. It is now time to stop hunting
17 zebras.
18 (Applause.)
19 DR. ALEXANDER: Thank you. Please hold your
20 applause until the last speaker has spoken. Will
21 speaker 47 please introduce yourself? Please state
22 your name and any organization you are representing

1 for the record.
2 DR. DAY: Yes. My name is John Day. I'm a
3 professor of neurology and pediatrics at Stanford
4 University. And I appreciate having the
5 opportunity to address the advisory committee to
6 provide my perspective on the importance of making
7 eteplirsen available for treating Duchenne.
8 I've received financial support from Sarepta
9 for scientific consultation. My travel to the
10 meeting was supported by the Make Duchenne History
11 Coalition, but I have no direct financial interest
12 in the outcome of today's meeting.
13 I direct the Stanford Neuromuscular Program,
14 Stanford Duchenne Comprehensive Care Center, where
15 we see Duchenne patients from a large part of
16 Northern California. For the preceding two decades
17 before moving to Stanford, I was director of the
18 neuromuscular program, the Paul and Sheila
19 Wellstone Muscular Dystrophy Center, and the
20 Duchenne Comprehensive Care Center at the
21 University of Minnesota, where I saw patients from
22 the Upper Midwest and where I also ran my own CLIA

1 certified neuromuscular biopsy lab.
2 I've rewritten my talks to basically focus
3 on specific issues the FDA brought up in their
4 review, so I won't be needing any of the slides.
5 First, regarding the adequacy of the control
6 group, it matches my own experience. During the
7 course of my career, I've diagnosed and cared for
8 250 boys with Duchenne muscular dystrophy, more
9 than 20 of whom had exon 51 skippable mutations.
10 Despite optimal care, none of those boys walked
11 beyond 12 years of age. This clearly differs from
12 the eteplirsen 201/202 experience where boys
13 continued to walk for 3 to 4 years of treatment at
14 ages greater than 12.
15 In addition to my experience with Duchenne
16 natural history, we have 4 subjects at Stanford
17 involved in current eteplirsen studies, all have
18 remained ambulatory, ages 9-11, and are functioning
19 well in multiple respects with no side effects.
20 Second, in terms of questions regarding
21 reliability of age of loss of ambulation, we can
22 agree with Dr. Farkas' contention that a placebo

1 arm differs from a natural history study. But my
2 experience is that boys try to keep walking as long
3 as possible and that the difference of several
4 years between walking and non-walking, by my
5 experience, mirrors the results in the Italian
6 registry, and the eteplirsen's results are striking
7 and meaningful.
8 Furthermore, in a slide of speaker
9 number 36, Stan Nelson, you can see a statistically
10 significant difference in the Duchenne Connect data
11 regarding the Kaplan-Meier curve for loss of
12 function of eteplirsen compared to steroids alone.
13 In essence, I'm convinced that eteplirsen
14 improves the course of Duchenne by multiple
15 measures, and I strongly urge its approval.
16 (Applause.)
17 DR. ALEXANDER: Thank you very much. Will
18 speaker 48 introduce yourself? Please state your
19 name and any organization you are representing for
20 the record.
21 MR. LOPEZ: My name is Roger Lopez, and I
22 represent the International Association of

1 Firefighters as the IAFF MDA national coordinator.
2 We have no financial interest in this.
3 The IAFF is a nonprofit labor organization
4 representing over 300,000 firefighters and
5 emergency medical service providers in the United
6 States and Canada. Our members serve cities,
7 towns, and fire districts in every state and
8 territory. Our members protect the communities
9 that are home to over 85 percent of the population
10 of the United States.
11 The IAFF is based in Washington, DC within a
12 network over 3200 local affiliates. For over
13 60 years, the IAFF has stood shoulder-to-shoulder
14 with the Muscular Dystrophy Association in the
15 ongoing fight against the more than 40
16 neuromuscular diseases that are claiming the lives
17 of our children and our fellow firefighters.
18 Through our Fill the Boot campaigns, the
19 IAFF has helped MDA fund the research that is now
20 resulting in the development of breakthrough
21 therapies for these devastating diseases. To date,
22 we are proud we have contributed over a half

1 billion dollars of funds to help find an end to
2 diseases like Duchenne, $26 million just last year.
3 Our commitment to this fight is unwavering.
4 This year alone, more than 162,000 of our
5 firefighters volunteered their time in more than
6 3000 events across the country to raise money to
7 support this mission.
8 But our hard work and dedication go beyond
9 our commitment to fill the boot. We are in this
10 fight at a personal level. Every year, many of our
11 firefighters from around the country dedicate a
12 week of their time to volunteer to MDA summer
13 camps. These are wonderful places where kids can
14 go to get a traditional summer camp experience
15 despite the challenges they face.
16 Last summer, many of our firefighters had
17 the chance to share the week with these amazing
18 children. I, myself, have participated every year
19 for the past 13 years. I look forward to it every
20 summer. It is truly a life-changing experience.
21 Through our many years of working with the
22 MDA and the families they serve, we understood the

1 impact of this disease, and we want to see
2 effective options for every one with Duchenne and
3 the other related diseases become available.
4 I am not here today as an expert on the
5 science, but we as firefighters want to take this
6 opportunity to express our support for finding
7 therapies that can improve and save the lives of
8 the people that we love, people living with
9 muscular dystrophy.
10 We have helped lead this fight for more than
11 half a century, and we are proud of the IAFF's many
12 contributions, and will continue this fight to
13 fulfill the promise from our earliest days of our
14 partnership to join forces and fight back until
15 cures are found.
16 I have 16 seconds left, and I want to relate
17 to the families, how important you all are to us
18 and that we've been doing this for 60 years, and
19 we're here for you. And we're going to be here for
20 you until we find a cure. Thank you.
21 (Applause.)
22 DR. ALEXANDER: Thank you very much. Will

1 speaker 49 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.
4 DR. CWIK: Good afternoon, I'm
5 Dr. Valerie Cwik, representing the Muscular
6 Dystrophy Association. I have no personal
7 financial relationship with the sponsor, but MDA
8 receives contribution for educational support and
9 conferences from a number of drug companies
10 targeting therapies for muscular dystrophy,
11 including Sarepta. And some of our board members,
12 because they have expertise in this field, from
13 time-to-time are paid to consult with drug
14 companies, again including Sarepta.
15 I'm pleased to be here today on behalf of
16 MDA and the thousands of Duchenne families that we
17 represent. At the outset, I'd like to share MDA's
18 optimism that there will soon be treatment options
19 to change the course of Duchenne muscular dystrophy
20 and that eteplirsen could be the first of what we
21 hope will be many new treatments for MDA families.
22 As chief medical and scientific officer at

1 MDA and as a neurologist and former MDA care center
2 director, I've worked with many families living
3 with Duchenne. I'm reminded that my 25 years of
4 medical specialty in the neuromuscular diseases is
5 about the same amount of time that the average
6 person with Duchenne can expect to survive, and
7 this is a reality that is unacceptable to MDA.
8 MDA has led the search for treatments and
9 cures for Duchenne for more than a half century and
10 will continue to do so until there is a cure.
11 Twenty years ago, we funded foundational exon
12 skipping research and follow-on studies that led to
13 the development of eteplirsen. And while not a
14 cure, the data indicates that the drug could slow
15 disease progression.
16 Many leaders in the Duchenne research and
17 clinical communities have voiced enthusiastic
18 support for eteplirsen, and as a science and
19 evidence-based organization, their support carries
20 great weight with us.
21 All of us at MDA, as well as our sister
22 organizations, scientific community, families and

1 supporters have been working tirelessly to see a
2 time like the present, a time when therapies could
3 be more than just a hope for the future. We are
4 all here for those living with Duchenne and the
5 people who love them.
6 It is time that treatment options shift from
7 being a goal to being reality. While the decision
8 of whether to approve a drug is ultimately a
9 regulatory science determination for the FDA, given
10 the support of Duchenne scientific and clinical
11 leaders, the support of the families we serve, the
12 urgent and unmet medical need, and the strong
13 safety data, we urge you to strongly consider all
14 of the tools available to the FDA to allow the
15 earliest possible access to eteplirsen. Thank you.
16 (Applause.)
17 DR. ALEXANDER: Thank you very much. Will
18 speaker 50 introduce yourself? Please state your
19 name and any organization you are representing for
20 the record.
21 MS. HICKMAN: My name is Chelsie Hickman,
22 and I'm reading a statement on behalf of

1 Shannon Dematteo, the mother of one of the 12 study
2 participants who started in 2011.
3 "On March 3, 2008, at 5 years old, our son,
4 Jack, was diagnosed with Duchenne muscular
5 dystrophy. Jack's doctor never described him as an
6 outlier, and as far as we could tell, he followed
7 the normal progression of Duchenne.
8 "When Jack was 8 years old, we began
9 traveling to Columbus, Ohio from Chicago every
10 Sunday for a Monday infusion in the eteplirsen
11 study.
12 "I've heard that the FDA thinks that the
13 benefit that the boys in the trial with Jack may
14 have seen was because they started steroids early
15 or their steroid dose or standard of care was far
16 better than those in the natural history group.
17 But I would like to let you know that Jack started
18 at age 6 and was dosed correctly for his weight.
19 He received stretching as physical therapy every
20 other week for about an hour and now swims once a
21 week, neither of which could be described as a
22 rigorous, intensive regiment.

1 "Never once, in the three-plus years of Jack
2 receiving eteplirsen has he had an adverse reaction
3 to it, not a fever, not a cough, not a headache,
4 nothing. In fact, most of the time, we noticed
5 that the day after his infusion is often one of the
6 best days of his week as far as his energy level
7 and his physical abilities.
8 "Because we understand Duchenne, we were
9 fully prepared to be taking care of a child who was
10 wheelchair-bound by the time he was 10 or 11. When
11 Jack was 11, he was playing on the school's
12 volleyball team.
13 "Our kids all go to Catholic school in a
14 very old building that's not ADA accessible. He
15 was able to walk up and down the stairs several
16 times a day, every day in school, until he was in
17 5th grade.
18 "Jack, at 13 and a half, is still declining
19 but at a much slower rate than we expected. He
20 needs help getting up from the ground, and he uses
21 a scooter or wheelchair to get around for distance.
22 But for the majority of his life, he is completely

1 independent. Like all of the 7th graders in our
2 neighborhood, he walks around with his friends to
3 go to the park, out to eat or just to hang out.
4 He's on the student council at school, is the
5 assistant coach manager for every one of the school
6 sports teams, and he has more friends than we can
7 count.
8 "Because of eteplirsen, Jack has been able
9 to enjoy a far more normal and active life than we
10 ever could have dreamed. We thank God every day
11 for our good fortune. We know Jack one of the
12 lucky ones, and we know that other boys, like Jack,
13 would benefit from being on this drug." Signed,
14 Shannon and Tom Dematteo.
15 (Applause.)
16 DR. ALEXANDER: Thank you very much. Will
17 speaker 51 introduce yourself? Please state your
18 name and any organization you are representing for
19 the record.
20 MS. LEFFLER: I'm introducing my son's video
21 testimony on his experiences on eteplirsen. We
22 chose to have him submit video testimony because we

1 didn't want him to come here and realize that his
2 access to eteplirsen was at risk.
3 Aiden, you see, is a warrior. In his
4 testimony, you'll see a series of videos of Aiden
5 trying to get into the car. At the start of the
6 study, I did not tell Aiden how long it might take
7 for eteplirsen to work because I did not want to
8 bias his performance.
9 The first video was taken over a month into
10 the study. Aiden is frustrated at this point
11 because he is convinced that the drug doesn't work.
12 Two weeks after this video was taken, in
13 fact, he asked me if he could quit the study
14 because he was tired of hospitals and needles
15 without seeing benefit.
16 Members of the advisory committee, please
17 watch my son regain function with your own eyes.
18 Ask yourself how it could be placebo-controlled or
19 placebo effect if he is convinced the drug doesn't
20 help.
21 Survey what you know about Duchenne and ask
22 yourself how likely this video would be if

1 eteplirsen doesn't work. It is not enough to
2 listen to our words and send us on our way. You
3 are charged with using our words to inform the
4 decisions that you make and hear our Aidens.
5 (Video played and transcribed.)
6 AIDEN LEFFLER: My name is Aiden and I'm 12
7 years old. I have Duchenne muscular dystrophy.
8 I've been on eteplirsen for only a little over a
9 year, 62 visits. I stopped being able to get
10 myself into our car about 9 months before started
11 eteplirsen.
12 I used to wait by the car door, and then mom
13 would pick me up in the arms and lift me into the
14 car. It's embarrassing at school being picked up
15 like that in front of friends. And then it all
16 changed.
17 I would like to show you some clips of how
18 life has treated me since I started this drug, at
19 the beginning of the trial, 5 months in and 7
20 months in. And it really has been changed.
21 (Pause.)
22 AIDEN LEFFLER: My mom was more than scared

1 I wasn't going to be able to walk anymore. But
2 then I started eteplirsen, and now I'm able to do
3 everything I was before.
4 Now, you'll see me downstairs playing soccer
5 for hours at a time. Now, I can use the car ramp,
6 now by myself. I taught myself. Thank you,
7 eteplirsen. Thanks for giving me a chance to be
8 normal, to do what I want to do.
9 I'd like to end my presentation with a video
10 of me playing catch with Russell Wilson,
11 quarterback with Seattle Seahawks.
12 (Laughter.)
13 AIDEN LEFFLER: Thanks to eteplirsen I'm
14 able to enjoy moments like this, moments that every
15 boy waiting for eteplirsen deserves.
16 (Applause.)
17 DR. ALEXANDER: Thank you very much. Our
18 final speaker is speaker number 52. If you could
19 introduce yourself. Please state your name and any
20 organization you are representing for the record.
21 MS. McLINN: My name is Laura McLinn. I
22 paid my own way here, and I have no financial

1 interest in today's outcome.
2 My 6-year-old son, Jordan, is a candidate
3 for exon skipping, but is not yet able to receive
4 the drug. On Thursday, I received a phone call
5 from United State Senator, Joe Donnelly. He asked
6 if I would read a letter that he and three other
7 senators wanted to share with you today. He's in
8 our home state of Indiana today and regrets that he
9 cannot be here personally. I won't have time to
10 read the entire letter, so I will share some key
11 points.
12 "In 2012, Congress provided additional tools
13 to facilitate new therapies intended to treat
14 persons with life-threatening and severely
15 debilitating illnesses, especially when no
16 satisfactory alternative exists.
17 "We write today to underscore the focused
18 efforts of Congress to provide for and encourage
19 accelerated review of promising therapies,
20 prioritize the patient perspective in evaluating
21 new drugs and treatments, and provide regulators
22 with flexibility to expedite evaluations of drugs

1 for life-threatening illnesses for not only
2 Duchenne but all rare and severe diseases.
3 "FDA regulations state that it is
4 appropriate to exercise the broadest flexibility in
5 applying the statutory standards. As members of
6 Congress, representing constituents who are
7 battling rare and severe diseases with unmet
8 medical needs, we wholeheartedly agree with this
9 viewpoint and we urge the FDA to ensure this
10 flexibility is applied in reviewing all candidate
11 therapies.
12 "The cost of unnecessary delays manifests in
13 terms of human lives. And therefore, urgency on
14 this matter to patients and their families is
15 absolute. Thank you for your attention to this
16 important matter."
17 This is signed by four United States
18 senators: Ron Johnson, Thomas Carper,
19 Joe Donnelly, and Dan Coats.
20 As you know, there are similar letters from
21 the United States Congress highlighting these
22 points, especially the requirement that the FDA

1 consider the perspective of patients during
2 regulatory discussions.
3 There seems to be a challenge with measuring
4 dystrophin. That doesn't mean it's not there. It
5 means maybe more work needs to be done in this
6 area, right? I mean really, we don't have a true
7 scientific piece of evidence that explains how we
8 even exist but we do exist, right?
9 (Laughter.)
10 MS. McLINN: Do we need a piece of
11 scientific evidence to proof the amount of
12 dystrophin? Your evidence is right here in this
13 room. And because of FDASIA, you are not only
14 allowed to use that evidence, but you have a lawful
15 and ethical responsibility to do so.
16 Every person in this room has been given a
17 shot at this thing called life. We didn't deserve
18 it, but God gave it to us anyway. There is no
19 lawful, moral, scientific, or ethical reason to
20 deny these well-deserved boys a chance to live
21 their lives and fulfill their own destinies. Let's
22 do the right thing. Let's make Duchenne history

1 today.

2 (Applause.)

3 **Questions to Committee and Discussion**

4 DR. ALEXANDER: Thank you very much,

5 speaker, and for all the speakers that participated

6 in the open public hearing. We'll now proceed with

7 the questions to the committee and panel

8 discussions.

9 I'd like to remind public observers that

10 while this meeting is open for public observation,

11 public attendees may not participate except at the

12 request of the panel.

13 I also want to remind the panel as there's

14 an extraordinary amount of information that we

15 could talk about and lots and lots of interesting

16 areas for discussion, so please, keep your

17 questions crisp. And for those that are responding

18 to questions, either on the part of the FDA or the

19 sponsor, please keep your answers crisp and concise

20 as well. Thank you.

21 So we'll move to the first question at hand,

22 which was provided to all of the panelists. The

1 question itself is to discuss the evidence
2 presented about dystrophin production, including
3 the following: A) the strength of evidence that
4 eteplirsen increased the amount of dystrophin in
5 muscles of treated patients relative to their
6 baseline; and B) the clinical meaning of the amount
7 of dystrophin observed in the muscles of
8 eteplirsen-treated patients, taking into the
9 consideration the range of amounts of dystrophin
10 known to be typically present in patients with DMD
11 and in patients with Becker muscular dystrophy.
12 I'll also point the panelists, there is a
13 little bit of discussion that precedes this actual
14 question that's posed, if that's helpful for you to
15 review again, but I think that we've heard the
16 content of that in the presentations from both the
17 sponsor and the FDA.
18 So with this, we'll open for discussion.
19 The first question, which is a non-voting question,
20 discuss the evidence presented about dystrophin
21 production.
22 Dr. Green?

1 DR. GREEN: Okay. I think there is moderate
2 evidence for dystrophin production. However, I
3 think it's more difficult than that because at the
4 end of the day, we don't really have a clue as to
5 how much is clinically significant.
6 We also, at least I don't, have a clue about
7 this dystrophin that's manufactured, whether it is
8 effective, the same or better than native
9 dystrophin. So I think it's a very difficult
10 biomarker.
11 DR. ALEXANDER: Thank you. I'm sorry.
12 Dr. Onyike?
13 DR. ONYIKE: If I recall from Dr. Farkas'
14 testimony earlier, it would appear that there are
15 some people who have very, very low levels of
16 dystrophin and much better clinical function than
17 you'd anticipate from that -- am I recalling that
18 correctly?
19 So it seems to me, therefore, that there
20 might not even exist the threshold of effect but
21 rather, it's possible that dystrophin couples in
22 some way that is indirect to function.

1 I recall that -- I think it was
2 Dr. Chamberlain and the gentleman also, the
3 investigator from Harvard, also suggested that the
4 levels of -- that it might take very low levels to
5 achieve a significant clinical effect.
6 Now, the question is whether that would be
7 universal or whether it would only apply to a
8 subset of individuals. And if so, what are the
9 other markers that might indicate or that might
10 predict how dystrophy links to clinical effect?
11 So in other words, it's ambiguous. I agree
12 with Dr. Green in that sense, that it's very
13 ambiguous.
14 DR. ALEXANDER: Thank you. And am I
15 understanding you correctly that you're pointing
16 out that it's ambiguous with regard to whether
17 there's a threshold effect or not, but also was
18 there a second part of that, what else may couple
19 with the absolute amount of dystrophin to produce
20 the clinical response that one sees?
21 DR. ONYIKE: Well, first of all, I suspect
22 that there may not be threshold per se or that the

1 threshold may vary widely perhaps on an individual
2 or in the subgroup way, and that we have no idea
3 what that range is. But it may very well dip very
4 low.
5 Does that clarify?
6 DR. ALEXANDER: Yes, thank you.
7 Dr. Kesselheim?
8 DR. KESSELHEIM: To me, a lot of the answer
9 to this question of whether there's an increased
10 amount of dystrophin in the muscles depends to a
11 lot of extent on the methods being used to assay
12 that. I guess I wasn't convinced or I'm still
13 questioning whether the biopsies that were taken
14 were the correct biopsies and why it was that the
15 two different muscle groups were compared. And I
16 was dismayed by some of the inconsistencies and the
17 availability of the comparative evidence.
18 So I think that because of those various
19 things, it makes it pretty hard to draw a firm
20 conclusion about point A.
21 DR. ALEXANDER: Thank you. Other comments?
22 Dr. Hoffman?

1 DR. HOFFMAN: Yes. I think there's plenty
2 of evidence that the mechanism of action for
3 eteplirsen is producing dystrophin. Both the PCR
4 testing, the immunofluorescence, and the Western
5 blot all have indicated, many times in all
6 different species, that mechanism of action.
7 DR. ALEXANDER: Thank you. Yes, I didn't
8 hear Dr. Kesselheim or others question the
9 mechanism of action. What I heard was that
10 conclusions about whether or not there's a large
11 amount produced depends upon the methods used to
12 assess this, and also some concern regarding
13 whether the biopsies were the correct biopsies or
14 not and concern regarding the quality of the
15 comparative evidence.
16 DR. HOFFMAN: I read the question as, is
17 eteplirsen producing --
18 DR. ALEXANDER: Can you speak into the
19 microphone more please?
20 DR. HOFFMAN: Yes. I think the question --
21 DR. ALEXANDER: I'm sorry. State your name
22 also for the record.

1 DR. HOFFMAN: Yes. Richard Hoffman. I
2 think there's plenty of evidence in all those
3 different testing methods that show that the
4 mechanism of action of eteplirsen is to skip
5 exon 51 and produce dystrophin. I don't think
6 there's any question about that. It's not only in
7 humans but in other species.
8 DR. ALEXANDER: Thank you. Dr. Ovbiagele?
9 DR. OVBIAGELE: Perhaps I'm not reading this
10 correctly, but as I understood it, one of the big
11 challenges here was the issue of not enough pre-
12 and post-treatment comparisons on the same
13 patients; so no matched baselines. And that's
14 exactly what the A question is asking.
15 So for me, there isn't the evidence there
16 because the comparisons were with other controls
17 but not necessarily the pre- and post. Is that
18 correct?
19 DR. FARKAS: Yes, that's the concern.
20 DR. ALEXANDER: Thank you. I'm transcribing
21 while we go. Other comments regarding question 1?
22 Ms. Gunvalson?

1 MS. GUNVALSON: I agree with Richard
2 that --
3 DR. ALEXANDER: I'm sorry. Can you please
4 state your name for the record?
5 MS. GUNVALSON: My name is Cheri Gunvalson,
6 and I agree with Richard that the issue was to
7 produce dystrophin, and we did produce dystrophin,
8 or the drug did, as Dr. Kunkel said. And I believe
9 we're seeing clear benefit from it. I know
10 hundreds of boys with Duchenne, my son included,
11 and you just don't see this clinical benefit.
12 DR. ALEXANDER: We will be discussing
13 benefit, but for right now we're focused strictly
14 on the dystrophin production in terms of the
15 strength of evidence, that the drug increased the
16 amount of dystrophin and also the clinical meaning
17 of the amount produced.
18 So do you feel that the amount produced is
19 sufficient to explain the clinical benefit?
20 MS. GUNVALSON: Yes, I do believe. And as
21 the physician down there said, we don't know the
22 exact amount. There are Becker boys that produce

1 very, very trace amounts that look very, very good.
2 We just don't know that.
3 So I don't -- for me, the fact that it
4 produced dystrophin and there are some boys and
5 young men with very scant amounts that do very
6 well, it's difficult to know the clinical benefit.
7 You know, I think we're all learning here,
8 not only the physicians and the FDA. This is a
9 learning process. There's never been a drug
10 approved. So that's my opinion.
11 DR. ALEXANDER: Thank you very much.
12 Dr. Woodcock?
13 DR. WOODCOCK: I would like to talk about
14 the order of this question. Question 1B, all
15 right, whether the clinical meaningfulness, you're
16 going to talk about that next as far as the
17 strength of the clinical data. However, what might
18 influence your assessment of whether the dystrophin
19 is actually clinically meaningful might be the
20 clinical data from the study or studies that were
21 done.
22 So if you're talking about this first,

1 you're going to have to think about what you think
2 about the clinical studies in relation to the
3 amount of dystrophin that has been produced, if you
4 follow me.
5 DR. ALEXANDER: Thank you. Yes.
6 Dr. Kryscio?
7 DR. KRYSCIO: Yes, the other Richard,
8 Richard Kryscio. Would like to ask Richard, since
9 you know these measurement techniques a lot better
10 than I do, where is the dose effect? I didn't see
11 any dose effect when they looked at 50 versus 30.
12 DR. HOFFMAN: Well, you're talking about a
13 dose ranging study, and really that hasn't been
14 accomplished. Maybe there's not enough of a
15 difference between 30 and 50 in animals. As far as
16 I know, in mice, they've gone up to 900 milligrams
17 per kilogram; and in dogs, I think they've gone up
18 as high as 200 milligrams per kilogram. And I
19 think at those higher doses, you would see the dose
20 effect.
21 I think one of the problems here is it's
22 been described by several people, the expression of

1 dystrophin in the muscle is regional or what's been
2 described as patchwork-type fashion that it's
3 produced after exon skipping. So if you're taking
4 a biopsy, it just represents a very, very small
5 part of the total musculature. And that particular
6 biopsy may not show as much, but there might be
7 other areas where there's very high amounts of
8 dystrophin produced, and that's where the
9 beneficial effects would be occurring.
10 That's just my opinion and from what I've
11 read.
12 DR. ALEXANDER: Thank you. Just a comment
13 that I'll make -- Caleb Alexander -- is just
14 the -- I'm surprised that there's not more
15 consensus. I accept that there may not be, but
16 it's surprising to me that there's not more
17 consensus, scientific consensus, regarding what
18 would constitute clinically meaningful levels of
19 dystrophin.
20 I will say that I think that the sponsor
21 question, the adequacy of Western blot data,
22 arguing that it really can't be compared with

1 published reports, but also made the case that in
2 prior reports of BMD, Beckers, that dystrophin
3 levels are between 2 and 100 percent.
4 The fact that there were also -- it sounds
5 as if early in the clinical development program,
6 there were estimates that dystrophin levels may
7 have increased as much as 20 to 50 percent, which I
8 think we would all argue or believe or feel would
9 be incredible results relative to, for example,
10 what we're seeing here.
11 Now, I'm referring to the actual
12 quantification with Western blot, and that clearly
13 was a pivotal event that appears to have had a very
14 profound impact on the subsequent decisions that
15 the sponsor and the FDA reached regarding the next
16 steps in the development program.
17 Dr. Romitti?
18 DR. ROMITTI: Yes. Paul Romitti. So in
19 looking at this and thinking about laboratory
20 methods in general, I think they're constantly
21 evolving. We are what we are today and we have the
22 best methods available.

1 While we may not know enough as we wish we
2 would with regard to dystrophin levels, I think
3 that after the instruction by the FDA to have three
4 blinded reviewers, I felt more confident with those
5 results, study sample aside, than I did with just
6 one reviewer, which I think is not quality science.
7 So I think even though the amount may have
8 been less and it may have been less striking than
9 originally reported by that one reviewer, I still
10 think that there is evidence here that there is a
11 difference. And the evidence may not be high, but
12 I think back to many studies that I'm involved
13 with, which are other studies where we're trying to
14 study biomarkers of exposure, they're challenging.
15 As the laboratory methods get better, we get
16 better at doing it. We can do it better in animals
17 than we can in humans. But we get better and we
18 get better in humans.
19 So I think given the state of the science
20 today, I think that there is enough evidence here
21 to say that with the re-analysis and the rereads,
22 that we do see some difference in dystrophin.

1 (Applause.)
2 DR. ALEXANDER: Dr. Dunn and then
3 Dr. Onyike, and then we may move onto the next
4 question, keeping in mind that we have seven, and
5 we're projected to be about 45 minutes to an hour
6 over at this point.
7 DR. DUNN: Billy Dunn, FDA. You mentioned
8 the difference. I just want to make sure I fully
9 explore that so we understand. When you mention
10 the difference, that obviously implies difference
11 in A and B. Can you just talk a little bit more
12 about what specifically you find the difference
13 between?
14 DR. ROMITTI: I'm referring to the
15 difference in the tables that were shown that
16 showed the single reviewer versus the three blinded
17 reviewers, and there was still a difference, if I
18 recall, of 17. There was a still a total of 17
19 overall as opposed to --
20 DR. DUNN: Right. I'm sorry. I didn't
21 actually mean the data in presentation as much as
22 the change from what dystrophin,

1 where -- obviously, you're referring to the 0.9
2 that was observed. And I think what I really want
3 to try and understand is what change, do you think,
4 that represented, what the comparison is.
5 DR. ROMITTI: From the data that we have
6 been given, the comparison is around 0.08, is what
7 I recall the comparison is.
8 DR. ALEXANDER: Can we see the table,
9 please? I wonder if that would be helpful in
10 clarifying this point.
11 DR. BASTINGS: Yeah. If you can pull
12 Slide 37 of FDA presentation?
13 DR. ALEXANDER: Dr. Nuckolls, do you want to
14 first try -- I'm sorry. Dr. Romitti, do you want
15 to try to address? I think the question was --
16 DR. ROMITTI: Okay.
17 DR. ALEXANDER: What I understood you saying
18 was that you have more confidence in the three
19 blinded reviewers than just one reviewer, and so
20 the amount --
21 DR. ROMITTI: So there are two different
22 measures here of dystrophin. There's the positive

1 fibers and then we have the PCR -- the Western
2 blot, excuse me. So I'm lumping both into my
3 discussion. If you would like me to reserve my
4 discussion for one, that's fine.
5 So this is what I'm meaning here for one and
6 the other is the 0.9 versus the 0.08 with the, what
7 I'll call FDA-accepted method of analysis being the
8 Western blot.
9 DR. ALEXANDER: Okay. Can you try one more
10 time, please? Just to be sure we have it straight
11 on the record, just making the point again.
12 DR. ROMITTI: Okay. I'm taking a look at
13 both measures that were used. The sponsor's
14 original endpoint was positive fibers. And I'm
15 looking at this, and I'm saying I was uncomfortable
16 with the original analysis given it lacks
17 replication. I was more comfortable that there
18 appears to be some kind of change here with the
19 re-analysis by the blinded reviewers for this
20 approach.
21 But I'm also commenting on the FDA's
22 suggestion of using Western blot as well to

1 quantify dystrophin. And with that and with the
2 unknown threshold, if there is one, for what is
3 enough dystrophin to see change, I think both
4 provide evidence there has been some change.
5 DR. ALEXANDER: Okay. Thank you very much.
6 Dr. Onyike?
7 DR. ONYIKE: Yes. I was just intrigued
8 earlier by the commentary. I think it was from a
9 gentleman who is my line of sight about how
10 dystrophin effect might transfer beyond specific
11 fibrils to their neighbors. But I don't fully
12 understand how this might work. So perhaps you
13 might elaborate.
14 DR. ALEXANDER: Who is the question for?
15 DR. ONYIKE: Well, it was a professor in the
16 audience who had talked earlier about evidence that
17 fibrils might generalize -- I mean, sorry, that
18 dystrophin levels --
19 DR. ALEXANDER: I'd like to --
20 DR. ONYIKE: Well, if you can't do it,
21 that's fine.
22 DR. ALEXANDER: Yes, yes. I --

1 DR. ONYIKE: I was intrigued by --
2 DR. ALEXANDER: Sure. Thank you. I mean
3 for the record, I'd like to have the question be
4 known, but I think in the interest of being sure
5 that we give due consideration to the remaining
6 questions, we should move on, unless Dr. Ovbiagele
7 has a final comment on this?
8 DR. OVBIAGELE: No. I just wanted to say,
9 it's one thing to talk about change, but the other
10 thing is I think be asked about the clinical
11 correlation. So whether there's change or not is
12 one issue.
13 But if you remember, if you looked up the
14 four individuals with the best 6-minute walking
15 times, there was actually no correlation. Two of
16 them had the highest levels of dystrophin and two
17 has the lowest levels of dystrophin.
18 So to answer that question, the clinical
19 meaning is not clear based on that.
20 DR. ALEXANDER: Okay. Thank you very much.
21 So my job is to try to summarize what I've heard,
22 and this included the following. There's moderate

1 evidence for production of dystrophin, though we
2 don't have a clue how much is clinically
3 significant, also hard to know if what is produced
4 is as clinically active as natively produced normal
5 dystrophin. There might not be a threshold effect
6 or the threshold may vary wildly among individuals
7 with no idea what the range is, but it may dip very
8 low.
9 The conclusion about whether or not there's
10 a large amount produced depends upon the methods
11 used to assess this, not convinced that the
12 biopsies were correct biopsies or not; dismayed at
13 the quality of some of the comparative evidence;
14 plenty of evidence to support mechanism of action.
15 The big challenge is that there's not enough
16 pre- and post-treatment comparisons on the same
17 patients, and this is what question 1A is focused
18 on. Comparisons were with other patients.
19 The issue was to produce dystrophin, and the
20 drug did do this. Believe that we are seeing clear
21 benefit and that the amount produced is sufficient
22 to account for the clinical benefit observed;

1 whereas, the dose effect, maybe not enough of a
2 range examined in doses, and that might account for
3 the absence of a dose response.
4 The biopsy represents a very small part of
5 the musculature and may not show you as much.
6 There may be other areas where there are very high
7 amounts of dystrophin produced.
8 Surprising that we're not further along in
9 figuring out what amount of dystrophin would
10 constitute a clinically meaningful response and
11 also surprised that there's so little consensus
12 about this.
13 More confidence in the 3 blinded reviewers
14 than just one reviewer. Although the amount made
15 may have been less and less striking than initially
16 reported by the single reviewer, there's still
17 evidence that there is a difference. And this was
18 referring to both the immunofluorescence, as well
19 as the Western blot.
20 Belief that there's a change in the
21 reanalyzed data over time, but comparing that with
22 the Western blot data provided is difficult. And

1 we are asked about the clinical correlation, as
2 well as change, and we're asked to evaluate not
3 only the change in dystrophin levels but also the
4 clinical correlation. And the final point that I
5 heard was that there was no obvious correlation
6 between the dystrophin levels and the change in the
7 6-minute walk test.
8 So Dr. Woodcock?
9 DR. WOODCOCK: Yes. When you move to the
10 next question, I'd like to have a conversation with
11 the committee about what you're voting on, so
12 you're clear about what you're voting on,
13 question 2, in this part of the discussion.
14 DR. ALEXANDER: Thank you. We'll be sure to
15 do that.
16 So for voting questions, we'll first be
17 discussing the questions, subsequently voting on
18 it, but I'll read now for you about the voting
19 process.
20 For voting questions, we'll be using an
21 electronic system. When we begin the vote, the
22 buttons on your microphone will start flashing and

1 will continue to flash even after you have entered
2 the vote.
3 Please press the button firmly that
4 corresponds to your vote. If you are unsure of
5 your vote or you wish to change your vote, you may
6 press the corresponding button until the vote is
7 closed. After everyone has completed their vote,
8 the vote will be locked in.
9 The vote will then be displayed on the
10 screen. The designated federal officer will read
11 the vote from the screen into the record. Next, we
12 will go around the room and each individual who
13 voted will state their name and vote into the
14 record. You're also requested to please state a
15 very brief reason why you voted as you did if you
16 want to. We will continue in the same manner until
17 all questions have been answered or discussed.
18 So the voting question that we're posed with
19 is, has the applicant provided substantial evidence
20 from adequate and well-controlled studies that
21 eteplirsen induces production of dystrophin to a
22 level that is reasonably likely to predict clinical

1 benefit?
2 Dr. Woodcock?
3 DR. WOODCOCK: Yes. This is the standard
4 for accelerated approval. So this would be a vote
5 on whether or not that surrogate endpoint of
6 dystrophin is reasonably likely to predict clinical
7 benefit.
8 So this is a question about approvability,
9 and my point is that you have to factor in the
10 clinical data in this discussion, what weight you
11 think it gives to the reasonably likely decision.
12 So you're talking about, first, whether
13 question 1A, which you already discussed, whether
14 or not dystrophin was increased.
15 Now, reasonably likely, as you've already
16 discussed and I've mentioned in my opening remarks,
17 there is no standard established. And for this
18 condition, there is no threshold established
19 because there's never been a drug to do this.
20 So people don't know. They've looked at
21 natural experiments such as Becker's, and you see
22 that there is a range of response as was said

1 earlier. So the question that you're being posed,
2 if you follow me, is does the clinical experience
3 in these trials, with these patients, lead you to
4 believe, if you believe dystrophin was increased,
5 that that increase is reasonably likely to predict
6 a clinical benefit?
7 Do you follow me? Okay.
8 DR. ALEXANDER: Are there clarifying
9 questions for Dr. Woodcock or other members of the
10 FDA regarding the question?
11 (No response.)
12 Okay. If not, then we'll vote now. So once
13 again, the question is, has the applicant provided
14 substantial evidence from adequate and
15 well-controlled studies that eteplirsen induces
16 production of dystrophin to a level that is
17 reasonably likely to predict clinical benefit?
18 (Vote taken.)
19 DR. ALEXANDER: Please vote again in case
20 you haven't. Although your vote only counts once.
21 DR. CHOI: Everyone has voted. The vote is
22 now complete.

1 DR. ALEXANDER: Thank you.
2 DR. CHOI: For the record, we have 5 yes,
3 8 no, zero abstentions.
4 DR. ALEXANDER: So we'll now go around and
5 briefly state our name and vote into the record, as
6 well as a brief rationale for why you voted as you
7 did. So we'll begin with the first voting member
8 on this side.
9 DR. HOFFMAN: Richard Hoffman. I voted yes
10 because of all the reasons I mentioned earlier.
11 DR. ALEXANDER: Can you briefly state those
12 very succinctly?
13 DR. HOFFMAN: By all the testing methods
14 that were used, PCR, Western blot,
15 immunofluorescence, I believe that there is proof
16 that dystrophin was produced and that eteplirsen
17 was responsible for it.
18 DR. ALEXANDER: Thank you. Please proceed
19 around the room.
20 DR. GREEN: Okay. Mark Green. I voted yes.
21 I believe that dystrophin is made by the drug. As
22 I said before, I'm very troubled by not

1 understanding a clinically significant amount. And
2 I'm not sure at what level I'm supposed to say
3 this, but I've been extraordinarily influenced and
4 impressed by the people who spoke about this drug
5 earlier and their observations.
6 (Applause.)
7 MR. DUPREE: To me --
8 DR. ALEXANDER: State your name please.
9 MR. DUPREE: Benjamin Dupree. Do I state
10 what my vote was? I voted yes, and the reason
11 behind that is that it appears to me, as has been
12 described by Paul Romitti, that there's a change.
13 And I think given the clinical results that were
14 described, it's reasonably likely to predict
15 clinical benefit.
16 DR. ALEXANDER: Please just continue around
17 the room.
18 MS. GUNVALSON: I'm Cheri Gunvalson, and I
19 voted yes. I believe the dystrophin was produced,
20 and that was what the goal was. And I believe it's
21 demonstrated in the clinical abilities of these
22 boys, that you don't regain lost milestones in

1 Duchenne, never.
2 (Applause.)
3 MS. GUNVALSON: And I think that the
4 qualitative data was good, and I would hope that
5 the FDA would require qualitative data on future
6 studies, because as a public health nurse who does
7 studies on populations, we look at quantified data
8 and quality data. And in the trends in the quality
9 data, you can almost find out more. So number of
10 falls I think is tremendous information on how a
11 drug is working.
12 DR. ALEXANDER: Thank you. Dr. Kryscio?
13 DR. KRYSCIO: Richard Kryscio. I voted no.
14 I guess I'm the first no vote. I voted no because
15 I don't think the studies were well controlled. I
16 was concerned with using different tissue samples.
17 I was concerned about a lack of correlation that
18 people who have little or no -- people who had
19 substantial problems clinically may or may not have
20 had a lot of the dystrophin actually produced.
21 Perhaps it's a measurement issue, but that's the
22 reason I voted no.

1 DR. ROMITTI: Paul Romitti. And I hit the
2 wrong button. I apologize.
3 (Applause.)
4 DR. ALEXANDER: I'm sorry. Please hold your
5 comments. Dr. Romitti?
6 DR. ROMITTI: Yes. I'm sorry. I must have
7 hit in between, so I apologize for the -- if I
8 can't change my vote, I understand.
9 DR. ALEXANDER: But just please, state for
10 the record what you intended to vote and your
11 rationale.
12 DR. ROMITTI: It's what I said before. I
13 think we do see some difference. Would I have
14 liked a better controlled study? Yes, but we do
15 see some difference. There was some evidence of
16 improvement in endpoints given the overall size of
17 the study.
18 DR. ALEXANDER: So for the record, your vote
19 is a yes?
20 DR. ROMITTI: Yes.
21 DR. ALEXANDER: Thank you.
22 (Applause.)

1 Dr. Nuckolls?

2 DR. NUCKOLLS: Glen Nuckolls. I voted no.
3 I think that Western blot comparison is the most
4 important for determining dystrophin level. And
5 the samples were done with samples from different
6 patients in different muscles. And I don't find
7 that this fits the definition of an adequate and
8 well-controlled study.

9 DR. FOLEY: Reghan Foley. And I voted yes.
10 I believe that Western blot in combination with
11 immunofluorescence are very important, and that
12 RT-PCR proves that drug was working by its intended
13 mechanism. And there's likely patchy dystrophin
14 expression, but I think the clinical efficacy seen
15 is likely secondary to that increase in dystrophin
16 expression no matter what degree increase was seen.

17 DR. KESSELHEIM: My name is
18 Aaron Kesselheim. I voted no. I wrote this
19 question down into four parts. There was the
20 applicant-provided part, the adequate and
21 well-controlled studies part, the induces
22 production part, and then the reasonably likely

1 part.

2 For me, I felt like the induces production

3 part was the easiest. It clearly does seem, to me,

4 to induce production. I felt like the studies that

5 were provided by the applicant were not adequate

6 and well controlled because of the problems that I

7 discussed earlier in terms of the sampling, and the

8 comparisons that were made, and the lack of

9 adequate comparators before and after, and the

10 staining issues that we went over before.

11 Then the final part is the question of

12 whether it was reasonably likely to predict

13 clinical benefit. I was moved a lot by the lack of

14 association between the findings from the results

15 in some of the clinical findings.

16 I think it is still an open question though,

17 and I think that it is possible that the drug does

18 work, but that the methods being used to test for

19 the drug, in this case, just weren't specific

20 enough to identify that.

21 DR. ALEXANDER: Caleb Alexander. I voted

22 no, and I had concerns about the techniques whereby

1 dystrophin was measured, the relatively modest or
2 very modest absolute amounts of dystrophin
3 produced, as well as the absence of more
4 scientifically rigorous selection and management of
5 controls to allow for, what I felt, would be
6 comparisons that would lead me to be more
7 confident.
8 DR. ONYIKE: Chiadi Onyike. I voted no. I
9 voted no because even granted -- and would be
10 willing to accept -- even if one is willing to
11 accept, and I am willing to accept -- for the
12 purposes of this question anyway -- that eteplirsen
13 led to some dystrophin production, but it's very
14 small. And it's still within the range of what
15 people with the disease have.
16 So with that in mind, it's very important to
17 have some sort of coupling between the dystrophin
18 production and the clinical effect. We don't have
19 that. So I can't get from dystrophin production,
20 even if I accept it, to any kind of clinical effect
21 without some understanding of a threshold or the
22 mechanisms -- if it were large amount, we would

1 have a different conversation but it's a very small
2 amount, too small to just go from dystrophin
3 production to clinical effect.
4 Now, as to whether there was clinical
5 efficacy, I think that's a separate issue in terms
6 of the clinical measures. I think it's a separate
7 question.
8 I do believe it is possible, for example,
9 for a medication to have an effect without you
10 knowing why. We have Tylenol, for example. We
11 have heparin. We don't know how they work. It
12 doesn't mean that we should throw them out.
13 So I'm not entirely sure that one should
14 lock the clinical effect to the dystrophin
15 production.
16 DR. ALEXANDER: Thank you.
17 DR. GONZALES: Nicole Gonzales. I voted no.
18 While I believe it is more likely than not that the
19 drug does produce dystrophin, the clinical data, as
20 presented with the use of historical control, was
21 very problematic for me and does not convince me
22 that whatever dystrophin is being produced is

1 demonstrated in a clear benefit clinically.
2 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
3 for many of the same reasons that have been
4 mentioned. I had problems with the techniques.
5 But even if I give a pass to the techniques and
6 there was some dystrophin production, I don't think
7 the study was well controlled. And most
8 importantly to the question that was asked, whether
9 the level was likely to produce a clinical benefit,
10 there was a lack of correlation between dystrophin
11 levels and the outcome. So that was a no for me.
12 DR. ALEXANDER: Thank you. So I'll briefly
13 summarize this for the record. Some of the votes
14 in favor were influenced by the reports of
15 individuals that provided comments during the open
16 public hearing. There was a comment that a change
17 of levels is present. This was felt to be
18 reasonably likely to predict clinical benefit.
19 There was a comment that dystrophin was
20 produced, and that was the goal and demonstrated in
21 the clinical abilities of boys, and you don't
22 regain lost milestones otherwise; support based on

1 the qualitative data that was provided, number of
2 falls.
3 Those voting no did so in part because of
4 concerns about the studies not being well
5 controlled, using different tissue samples, lack of
6 correlation between clinical progress and changes
7 in dystrophin produced, perhaps a measurement
8 issue.
9 There was a comment that one does see some
10 difference, some evidence of improvement in
11 endpoints based on the size of the population.
12 Western blot comparisons are most important, were
13 felt to be most important by a panelist. Samples
14 were done from different patients with different
15 muscles and doesn't fit the definition of adequate
16 and well-controlled study.
17 PCR suggested the drug is working by
18 intended mechanism, so a belief that the clinical
19 efficacy was likely due to differences in
20 dystrophin seen. Another panelist pointed that
21 there was evidence of induction, or production, I
22 should say, but the studies, once again, that were

1 provided by the applicant were not felt to be
2 adequate and well controlled.
3 With respect to whether or not these were
4 likely to be -- the dystrophin change was
5 reasonably likely to be predict clinically benefit,
6 the panelist was moved by the associations
7 presented but thinks it's an open question,
8 possible that it works, but the methods need to
9 test for this weren't specific enough, and so that
10 panelist voted no.
11 Concern about the quality of dystrophin
12 production data, about the techniques that were
13 used and the absence of more rigorous controls,
14 very small amounts of dystrophin and the range of
15 what people with the disease have untreated,
16 important to have some coupling between dystrophin
17 production and clinical effect.
18 Even if one accepts the dystrophin
19 production, hard to get from there to clinical
20 effect. If it was a very large amount of
21 production, we'd be having a different
22 conversation.

1 Another panelist, once again, more likely
2 than not that the drug produces dystrophin but the
3 clinical data are very problematic and not
4 convinced that the dystrophin that's produced is
5 generating the benefit that we see. And the final
6 panelist commenting problems with techniques, and
7 even if this is accepted, here again, the study
8 wasn't well controlled. And even if so, lack of
9 correlation between levels and outcomes.
10 With this, we'll move on to
11 question number 3, which is a discussion question.
12 Discuss the strengths and weaknesses of the
13 clinical evidence of efficacy provided by
14 study 201/202 with particular consideration of the
15 design of the study, sample size, statistical
16 methods, general concerns regarding comparison to a
17 historical control group, specific concerns with
18 respect to comparability of these two groups; in
19 particular, how motivational factors and
20 differences in assessment of physical performance
21 outcomes may have affected the 6-minute walk
22 endpoint and other endpoints, and any other issues

1 that you think may be important.
2 So we have a few moments for discussion
3 here. Once again, please keep your comments or
4 questions very crisp and focused on this question
5 at hand.
6 Ms. Gunvalson?
7 MS. GUNVALSON: I've seen a lot of 6-minute
8 walk tests, and I can honestly say that these boys
9 know what's going on. They know they're being
10 timed. They know this is a deadly disease.
11 They're on the internet. I can honestly say I've
12 not seen a boy motivated to do his best, and so
13 that's my opinion.
14 As far as -- yes, I just don't -- I know
15 what coaching is about. I have kids and athletes,
16 but you can't coach these kids to walk faster.
17 They have this waddle gait that if you push them to
18 go faster, they fall. It's just not possible. I
19 mean, it's like a balance beam how they do it, and
20 they go to the best of their ability.
21 DR. ALEXANDER: Thank you. Dr. Green?
22 DR. GREEN: Well, I think we all agree that

1 placebo controls are often flawed, but historical
2 controls are worse. And that was so well pointed
3 out in Dr. Temple's discussion on historical
4 controls.
5 So the data, my yes vote had to do with
6 external influences that I believe were
7 significant. But the way the study is designed, it
8 gives me very little comfort.
9 DR. ALEXANDER: Thank you. And I'll just
10 make a comment. Caleb Alexander. One contrast
11 that I wanted to underscore that I noted was the
12 difference and the conclusions that one reaches
13 when one looks at individual trajectory level as a
14 function of age at enrollment. And we saw several
15 analyses, I think three analyses, for the
16 historical controls and then three for the synergy
17 data by the FDA that provided this type of analysis
18 that are following individual patients over time as
19 a function of their age at study enrollment.
20 I did note that the sponsor had at least one
21 slide that had information that wasn't just means
22 or averages but actually allowed for individual

1 level trajectories, although even this slide only
2 looked at the 6-minute walk test as a function of
3 length of treatment, not patient age.
4 So I just wonder whether there's
5 information -- and so that seems, to me, to be a
6 really important set of slides and ones that point
7 in a different direction than if one looks at plots
8 of the primary outcome as a function of study
9 enrollment alone.
10 Dr. Gonzales?
11 DR. GONZALES: Nicole Gonzales. I just had
12 a comment. Just reading the data from Sarepta,
13 every single secondary clinical endpoint seemed to
14 be so positive. And listening to the testimonials
15 and the experiences of the boys and the families,
16 it just seems to me that had there been a true
17 placebo group, that the differences would have been
18 so striking and that the study may have even been
19 stopped soon. I'm trying to understand why there
20 wasn't an adequately powered placebo group.
21 DR. GORDON: Someone else has their mic on.
22 DR. ALEXANDER: Just one minute, please.

1 Does the sponsor want to respond to a
2 particular question about the absence of a placebo
3 group?
4 DR. KAYE: Yes, just to be able to address
5 to that about the placebo. So I think just to be
6 clear, I think when we had initially done the
7 phase 2 study, there wasn't enough drug at that
8 time. We didn't have the ability to manufacture
9 until almost two years later. So this was designed
10 as a phase 2B.
11 When we had enough drug to actually do a
12 placebo-controlled trial, because of the response
13 to the fact that this drug produced dystrophin and
14 also the clinical response, there really wasn't a
15 possibility at that time to be able to really do a
16 formal placebo-controlled trial.
17 This was exactly the same problem I had with
18 my Myozyme that you heard about earlier from
19 Dr. Temple. We had to make a decision at that time
20 what was the in the best interest of patients, and
21 we decided to do the external control, which is the
22 next best thing.

1 If I can have the slide up, one of the
2 things that we did -- and I agree --
3 DR. ALEXANDER: I'd like to move on,
4 actually. Thank you.
5 DR. GORDON: Okay.
6 DR. ALEXANDER: Thank you very much.
7 Dr. Onyike?
8 (Audience groans.)
9 DR. ONYIKE: I think when we have what I
10 perceive as a weakness on the biological
11 plausibility front and you have a small sample and
12 a control group that is not optimal, and when you
13 look at the effect of age corrections on the
14 outcome, the 6-minute walk test, you do want some
15 validity.
16 But when you turn to the 10-minute walk/run
17 results, or to the sit/stand, and to all the other
18 things that should provide convergent validity
19 regarding the outcome, what you find is that you
20 don't find any positive results.
21 So across the board, if a drug is effective,
22 given its pharmacologic effect, it should have

1 effect on multiple outcomes, not just the single
2 one. And that isn't happening in this data, so
3 that's my one problem I have.
4 Now, in terms of the testimony from the
5 families, what really struck me is that a lot of
6 the testimonies were about -- there was a picture.
7 I think it was Austin who is stacking cans, and
8 that's upper limb strength. And you look at -- all
9 the outcomes in this study were about limbs, about
10 the limbs or the trunk. And there is no study
11 outcome that's about upper limb strength or grip,
12 and I think that is a very unfortunate thing about
13 outcomes assessment in this field in general.
14 You want something that's tangible to
15 quality of life. You want something else that
16 accounts for the distribution of effects across the
17 various muscles, and without upper limb testing,
18 you don't have that.
19 DR. ALEXANDER: Can I just ask for you to
20 clarify the first comment that you made? What I
21 understood you to say is that you have concerns
22 about biologic plausibility because the drug isn't

1 having an effect on multiple outcomes. But can you
2 specify what you mean by that?
3 DR. ONYIKE: Let me clarify. When I'm
4 talking about plausibility, I'm going back to the
5 dystrophin. If the dystrophin data is not decisive
6 and you have a clinical outcome that arises from
7 comparisons with a suboptimal control and that
8 wilts under age correction, you need all the other
9 outcomes to line up in the same direction for the
10 single outcome to be considered a valid measure of
11 efficacy.
12 Now, it turns out that none of the other
13 outcomes, as depicted in the FDA analysis, lined up
14 with a positive effect.
15 Now, when you listen to the testimony from
16 the families, one of the things that was
17 highlighted is opening cans, opening packages,
18 lifting things, and none of that is captured by the
19 NSAA, or the 6-minute walk test, or the 10-minute
20 walk test.
21 So you have an unfortunate discrepancy
22 between what the families are describing as

1 tangible benefits and what is actually measured.
2 We're not even talking about negative measurements
3 now. We're talking about non-measurement of areas
4 of function that might have delivered some clarity
5 about the effects of this drug.
6 DR. ALEXANDER: Okay. So you're questioning
7 the biological plausibility and making the point
8 that one doesn't have a lot of dystrophin
9 production, and then reporting that, in that case,
10 that one would want all of the outcomes to line up.
11 But does the sponsor not present a case for
12 the outcomes being consistently positive? By what
13 basis are you deciding or the claiming that the
14 outcomes don't line up?
15 DR. ONYIKE: So when you look at slides 92
16 through 94, and when you look at 87, 88 --
17 DR. ALEXANDER: Can we see one or two of
18 these just to help us, remind us what this covers?
19 DR. ONYIKE: So 87, if we can look at 87, it
20 covers both the NSAA and the 6-minute walk test.
21 Slide 88 covers the rise time. And all of these do
22 not show a difference between the groups when

1 plotted as a function of age of the subjects.
2 So basically, outcome after outcome after
3 outcome is lining up as no effect, when
4 age-corrected. So there's no validity to
5 the -- you can't anchor claims of benefit on one
6 outcome when the rest of them are not falling in
7 line, particularly when your biological
8 plausibility and your control groups are subject to
9 question.
10 DR. ALEXANDER: Okay.
11 DR. ONYIKE: But I feel that there's an
12 inadequate measurement of treatment effect to begin
13 with because there's no measurement of upper limb
14 strength.
15 DR. ALEXANDER: Okay. Thank you. This is
16 Caleb Alexander. If you can leave the slide for a
17 minute, I'd like to give the sponsor a chance,
18 because this is the second time that this type of
19 analysis has been raised during this question
20 discussion.
21 So the question for the sponsor is whether
22 or not you considered or if you could help the

1 panel interpret the data that's presented here or
2 in slide 66, which precedes it, I believe. But
3 these all show a similar analysis of individuals
4 over time stratified by age. And the request is
5 just to help us interpret -- provide for us your
6 interpretation of what these data represent.
7 DR. KAYE: So if we just look at the rise
8 time -- and Dr. McDonald had described it -- what
9 was recorded is when it was really the ability to
10 rise. So those boys with the higher rise times had
11 with support. So that wasn't what we did in the
12 analysis; it was just the ability to rise. And
13 they were all less than 75 seconds.
14 If I could have a slide up --
15 DR. ALEXANDER: I'm sorry. Just --
16 DR. KAYE: Oh.
17 DR. ALEXANDER: This is another example of
18 that, if you could provide -- sort of help us
19 understand how these types of analyses complement
20 those that look at the effect over time rather
21 individuals plotted out over the course of -- based
22 on age.

1 DR. KAYE: Sure. Well, I really think the
2 main difference, though, is we're also looking at
3 the time on treatment. So if we were looking at
4 two external control groups and trying to see what
5 the difference was, then I think the age. What we
6 try to do is match up the baseline ages, 6-minute
7 walk test, all of the other parameters, the steroid
8 use, and then look at what is the time on therapy.
9 What this doesn't really show is what is the
10 ability -- what's the change we see in response to
11 the treatment. And I think when we look at that,
12 that's where we're able to see the treatment
13 benefit.
14 I think getting back to the question as far
15 as what do we see as far as other things, we did do
16 grip strength, both left and right, for 4 years,
17 and we did not see any decrease in that. That was
18 one of the exploratory measurements that we used.
19 We also looked at pulmonary function over
20 4 years, and as you heard, that's an important
21 event. And the pulmonary function should go down
22 anywhere from 5 to 8 percent per year. Every study

1 that's ever been done, that's with or without
2 steroids.
3 This study showed 2.5 percent per year. And
4 again, if we look that cumulative data and looking
5 at all of the information about -- looking at the
6 number of boys -- slide up please -- again, looking
7 at the treatment difference, if we look at this in
8 regards to what we see, we always see it in
9 benefit of treatment.
10 So 6-minute walk test, you heard about.
11 Loss of ambulation, it's even more. There was a
12 difference, but it was always in favor of
13 eteplirsen or the North Star and the ability to
14 rise, and then also what I just mentioned was the
15 pulmonary function.
16 So if we look at it from that
17 perspective -- and I think it is important not to
18 just look at the difference of ages because you
19 can't judge the boy at an age, what you've heard
20 from Dr. McDonald. It's how long are they walking,
21 what is their ability to rise, all of those
22 factors, how much steroids were they on.

1 So I think it's not a fair comparison to
2 just look at the age because a boy at age 11 who's
3 walking 600 meters is very different from a boy at
4 age 11. So what we try to do is make this
5 comparison at baseline when we started the
6 treatment. That's how every study is always done
7 because you have to look at what's the time on
8 drug. And I think when you do that, it's always in
9 favor of eteplirsen. And I think that's the
10 important thing that has to be done.
11 We appreciate the small size of the study,
12 but I think if you look at the totality of the
13 data, including the upper extremity function, it's
14 always in favor of eteplirsen.
15 DR. ALEXANDER: Thank you very much.
16 Dr. Gordon, did you have comment? And then
17 I think we'll just have one more, and we'll move
18 on.
19 DR. GORDON: The sponsor wanted to make an
20 additional comment.
21 DR. ALEXANDER: Can you speak into the
22 microphone? I'm sorry. Your comment?

1 DR. GORDON: Sure. The sponsor had asked me
2 to make a comment.
3 DR. ALEXANDER: I see. Dr. Bastings and
4 then Dr. Kesselheim.
5 DR. BASTINGS: Yes, I think I heard Dr. Kaye
6 make a comment that the kids were helped when they
7 were attempting to rise. You mentioned that there
8 was some help provided. I would like him to expand
9 on that a little bit.
10 DR. KAYE: Yes. So when we looked at the
11 rise time, I think one of the things that obviously
12 we wanted to make sure is that we did it exactly
13 the same way. So when the rise time was done, it
14 was the ability to rise independently, because if
15 you're hanging on to a chair or if you're hanging
16 on to the wall and you're getting up, it will take
17 a longer period of time.
18 So we specifically wanted to make sure that
19 we did the rise time from the external control to
20 our eteplirsen-treated boys in exactly the way. So
21 when you look at that -- and again, all of these
22 boys who got up did it in less than 25 seconds;

1 they all did it unaided. And then when you do that
2 exact comparison, then it's over half of the boys,
3 55 percent, were able to do that unaided compared
4 to 12 percent.
5 What was shown in that graph is the boys
6 from the external control who had lost the ability,
7 their rise time wasn't included, so it was just the
8 boys who -- so we actually tried to measure the
9 boys who could walk unaided, so it was a
10 difference.
11 I think that's really the focus, is that
12 what is the difference. When you do an apples-to-
13 apples comparison, you do see a difference.
14 DR. ALEXANDER: Okay. So just to clarify,
15 were the boys -- do the rise times uniformly
16 reflect unaided rise times or is some of them
17 aided --
18 DR. KAYE: Yes, that's correct. All of them
19 that are unaided that are used in this analysis.
20 DR. ALEXANDER: So does that answer your
21 question, Dr. Bastings?
22 DR. BASTINGS: Yes. So you're referring to

1 the rise time that were shown on slide 88 of the
2 FDA presentation?
3 DR. KAYE: That's correct.
4 DR. BASTINGS: Like when we have 40-,
5 45-second rise times, there was no help provided?
6 DR. KAYE: No, no. Those 45-second rise
7 times, they were using external support. That's
8 the difference. So in other words, when we looked
9 at the boys, what we looked at here is could they
10 walk unaided, and that wasn't recorded for the boys
11 in the external control. And maybe Dr. McDonald
12 can just explain it.
13 DR. BASTINGS: I don't think this
14 information was provided in the NDA.
15 DR. ALEXANDER: Okay.
16 DR. McDONALD: Could I just clarify this
17 data? This data is based on the North Star
18 subscore of whether you can perform the rise
19 ability independently or in an impaired fashion, or
20 if you cannot perform it independently; you've lost
21 the function.
22 So at 3 years, 55 percent of eteplirsen

1 treated patients have continued independent ability
2 to perform the rise ability, whereas only 8 percent
3 of the external controls.
4 Now, we made the point that as a prognostic
5 endpoint, it's really the loss of rise ability;
6 it's not how long it takes you to do the rise test.
7 It doesn't matter whether you're zero to 5 seconds,
8 5 to 10 seconds, or even greater than 10 seconds;
9 that's not prognostic for loss of ambulation. It's
10 the loss of rise ability, which this data captures
11 based on the North Star subscore of independent
12 rise time.
13 DR. ALEXANDER: Okay. Thank you very much.
14 I'll try to summarize what I've heard
15 regarding question number 3. There was a
16 comment -- and the record will reflect a more
17 accurate capture of everything because there was a
18 fair amount that was discussed.
19 But there was a comment regarding boys
20 knowing what's going on, a comment regarding
21 concerns about placebo controls often being flawed,
22 concern with regarding historical controls often

1 even being more flawed as represented by or
2 demonstrated by Dr. Temple's presentation.
3 There was a comment regarding the fact that
4 every secondary clinical endpoint seemed so
5 positive and listening to the experience of boys
6 and their families so positive. And if there had
7 been a placebo group, the panelist felt that the
8 study would have been stopped, yet they queried why
9 a placebo wasn't done.
10 The answer provided was that there wasn't
11 enough study drug available, and then at the point
12 when there was enough available, it wasn't possible
13 because of conclusions that had been reached
14 regarding the assays on dystrophin at the time.
15 There was a comment regarding the results
16 not being biologically plausible because we don't
17 have a lot of dystrophin. And especially in that
18 setting, one would want all of the other outcomes
19 to line up with very clear evidence of efficacy,
20 and that one doesn't have this, based on the FDA's
21 analyses such as in slides 87, 92-94, all of which
22 raise concerns or failed to show a

1 significant -- I'm saying not statistically
2 significant but rather failed to show a large or
3 observable qualitatively significant difference
4 between the groups.
5 The family testimony includes outcomes that
6 were not captured by the measures assessed, and
7 this was felt to be unfortunate and an unfortunate
8 discrepancy between what families were reporting
9 and what was actually measured.
10 There was encouragement to -- the sponsor
11 was queried regarding the analyses, but that the
12 FDA provides examined patients over time stratified
13 by the age at which they started treatment or
14 entered the historical control, and the sponsor
15 felt that these analyses don't show the change that
16 we see in the response-to-treatment; that one can't
17 just look at the patient age but has to look at the
18 time on therapy.
19 The sponsor also commented that pulmonary
20 function should go down 5 to 8 percent a year, but
21 didn't. I presume I was understanding correctly.
22 And the same with grip strength, and that these do

1 support the variety of additional outcomes that
2 were assessed.
3 The sponsor provided their analyses
4 suggesting that NSAA, the North Star assessment,
5 and ability to rise, and 6-minute walk test, all in
6 favor of the study drug based on their analyses,
7 and that kids were helped.
8 Then there's some uncertainty, a little bit
9 of unclarity on my part regarding whether or not
10 assistance was provided to kids and what
11 constitutes assistance, whether this was mechanical
12 devices or human help and the like, but that can be
13 clarified. And I'll just note that ambiguity in my
14 mind for the record.
15 With that said, we'll move to question 4,
16 which is a voting question. Were decisions to
17 administer the 6-minute walk test versus
18 conclusions that the patient could no longer walk
19 sufficiently objective and free of bias and
20 subjective decision-making by patients, their
21 caregivers, and/or healthcare professionals to
22 allow for a valid comparison between study patients

1 in studies 201/202 and an external control group?
2 So we'll move to voting on that now.
3 Once voting is concluded, we'll begin again
4 with -- well, why don't we begin at this side of
5 the table this time, to my left, once voting is
6 concluded. And just for the sake of time, rather
7 than my calling on you, please just state your name
8 into the record and your vote, and a brief
9 rationale after the person immediately to your left
10 has provided their information.
11 DR. HOFFMAN: [Inaudible - off mic.]
12 DR. ALEXANDER: Yes, C is -- I'm sorry.
13 D is abstain. So yes is B, like boy; no is C, like
14 Charlie; and D, like dog is abstain.
15 DR. HOFFMAN: [Inaudible - off mic.]
16 DR. ALEXANDER: So let me just read the
17 question just to be clear. The voting question is,
18 were decisions to administer the 6-minute walk test
19 versus conclusions that the patient could no longer
20 walk sufficiently objective and free of bias and
21 subjective decision-making by patients, their
22 caregivers, and/or healthcare professionals to

1 allow for a valid comparison between patients in
2 studies 201/202 and an external control group?
3 So if you believe that the decisions were
4 sufficiently objective and free of bias and
5 subjective decision-making, you would vote yes.
6 And if you believe they were not sufficiently
7 objective and free of bias and subjective
8 decision-making, you would vote no.
9 (Vote taken.)
10 DR. ALEXANDER: Please enter your vote one
11 final time. Press the button firmly.
12 DR. CHOI: Everyone has voted. The vote is
13 now complete. For the record, we have 5 yes, 7 no,
14 1 abstention.
15 DR. ALEXANDER: So we'll begin with
16 Dr. Ovbiagele.
17 DR. OVBIAGELE: Bruce Ovbiagele. I voted
18 no. I'll just be quick. Two reasons. Number 1,
19 of course, it was open label. I would have loved
20 to see a blinded adjudication of the outcome. That
21 would have at least helped a little bit.
22 Then, the other issue was in the control

1 groups themselves, it seemed as if in some
2 situations, patients were deemed unable to do the
3 6-minute walk test, which was not necessarily
4 appropriate in some situations. So I didn't think
5 it was necessarily objective.
6 DR. ALEXANDER: I'm sorry. Can you repeat
7 the second point? The first you made was about
8 open label and blinded adjudication. But what was
9 the second point?
10 DR. OVBIAGELE: The second point was about
11 in some situations, for the control patients, they
12 were deemed not able to do the 6-minute walk test.
13 And in those cases, it might not have been
14 appropriate for them to have been deemed
15 inable [sic] to do that -- unable to do that.
16 DR. GONZALES: Nicole Gonzales. I voted no.
17 For me, this has nothing to do with motivation. I
18 think it's crystal clear to me that boys are
19 extremely motivated to walk. And for me, this has
20 to do with the difficulties with using a historical
21 control, as has been demonstrated, not just in the
22 neurology but in all of medicine and all of the

1 biases that we cannot measure.
2 DR. ONYIKE: Chiadi Onyike. I voted yes. I
3 believe that what -- even though it's true that one
4 can't say that it was very systematic with respect
5 to looking at the study versus looking external
6 controls or that you can argue uniformity and
7 ascertainment of the scores, I don't think that the
8 magnitude of error would be enough to have
9 distorted the study outcomes if it were not for the
10 small sample size and other key problems.
11 DR. ALEXANDER: Caleb Alexander. I voted
12 no. I had concerns primarily about the -- well,
13 concerns both about the potential ways that the
14 controls may not have been exchangeable, comparable
15 with the treated patients, and these can be very
16 subtle.
17 Really, the impact of this is unknowable at
18 this point, so it's not so much that I'm convinced
19 that they're different as that it's unknowable, the
20 magnitude of difference that may have been present.
21 So that was my primary concern.
22 DR. KESSELHEIM: Aaron Kesselheim. I

1 abstained. With all due respect, I didn't think
2 this was a very good question, the way it was
3 written, and I had trouble interpreting it in order
4 to make a firm yes or no answer.
5 I felt like I was convinced through the
6 course of the day today that the 6-minute walk
7 test, though it is a subjective measure, it could
8 be a valid intermediate endpoint. But I had
9 trouble with the context in which it was used and
10 the results that came up in regard to the
11 historical control. I felt like it was more
12 appropriate to address that in the seventh question
13 as opposed to this question.
14 So because I couldn't exactly -- because I
15 agree with part of the question but not another
16 part of the question, I chose to abstain.
17 DR. FOLEY: Reghan Foley. I voted no due to
18 the problems with historic controls and seeing that
19 there were patients for whom there had been times
20 were at 10-meter walk or run but no time for the
21 6-minute walk.
22 I just think that the most important issue,

1 really, is the preserved ambulation and ability to
2 rise, which is kind of, to me, incontrovertible
3 evidence. But with this data with historic
4 controls, it was hard to control for other sites
5 and historically.
6 DR. NUCKOLLS: Glen Nuckolls. I voted no.
7 The predetermined selection criteria for the
8 control group were not sufficient to control for
9 biases. And since it's an open label, and I also
10 agree with your point about subjects that had a
11 12-second, 10-meter walk but were listed as
12 non-ambulatory, these caused me to question the
13 objectivity and comparability of a 6-minute walk
14 test.
15 DR. ROMITTI: Paul Romitti. I wavered
16 between yes and abstain. Just for the record, I
17 did push the correct button this time. Reason
18 is -- a couple of reasons, one, a fellow panel
19 member talked about upper body strength, but I
20 heard testimonies from more than one child who said
21 they were still walking after being on the drug.
22 So there was also measures of lower strengths, so I

1 do think there was consistency there.
2 The biggest problem I have with this -- and
3 I took the question literally, which is why I gave
4 it a yes. After working for a decade with a
5 30-year cohort of patients with Duchenne and Becker
6 muscular dystrophy, I believe these patients will
7 do anything they can to maintain their mobility,
8 and I don't think there are any extra motivated to
9 do so.
10 I think the other thing is, is I think we're
11 just losing a bit of grasp here on the
12 heterogeneity of this condition. And so in
13 analyzing data by age of the subject I think is
14 inappropriate.
15 I think it's more appropriate to look at
16 disease progression. After seeing after symptom
17 onset can happen at 2 years for some and 5 years
18 for others, I don't think that's the way to go. So
19 I was not convinced by the evidence that the FDA
20 presented by year, and I think it's more
21 appropriate to go by the stage of development where
22 the child is.

1 DR. KRYSCIO: Richard Kryscio. I voted no.
2 I was disappointed that the data was not analyzed;
3 the way the subjects were randomized, its
4 delay-start designed. They introduced historical
5 controls; I'm not convinced that they are
6 necessarily comparable. They had problems, as were
7 mentioned, throughout the day.
8 My real problem is the endpoint itself. I
9 mean, it just looks at the lower body; it doesn't
10 look at the upper body. And we've heard many
11 comments about upper body strength versus lower
12 body strength.
13 There are a lot of better measures. There
14 are diseases where you have more of a functional
15 rating scale. Take a look at ALS, which has
16 similar problems with people losing ambulatory
17 status. They have well-designed trials with lots
18 and lots of patients with a well-accepted endpoint.
19 This is not a good primary endpoint where
20 you have a floor effect when people can't walk, and
21 statistically, it just doesn't make sense to try to
22 average those numbers in the plots. Those are

1 called spaghetti plots in the statistical
2 literature.
3 MS. GUNVALSON: I'm Cheri Gunvalson, and I
4 voted yes. I believe that there was a
5 differential, and it has also demonstrated in the
6 boys that showed us upper body and lower body
7 increases.
8 I think the FDA should require a
9 non-ambulatory arm in every Duchenne trial because
10 there are a lot of things that need to be studied.
11 If a drug is approved, and non-ambulatory boys who
12 are on a cohort of cardiac meds and things like
13 that, that should be looked at in a trial setting
14 for safety, not after a drug is approved. And
15 also, there are things you can measure but safety
16 is a main factor too.
17 I agree with Dr. Day who spoke about -- he's
18 a neurologist who's seen hundreds of boys with
19 Duchenne. His data is similar to the historical as
20 how boys decline, which there was a study done by
21 UCLA. So I --
22 DR. ALEXANDER: Thank you. Thank you.

1 MR. DUPREE: Benjamin Dupree. I voted yes.
2 DR. ALEXANDER: Can you just speak into the
3 microphone a little bit more? Thank you.
4 MR. DUPREE: Sorry. Benjamin Dupree. I
5 voted yes, the reasoning being that, specifically,
6 with the 6-minute walk test, I think that given how
7 much boys with muscular dystrophy want to continue
8 to walk, that I just don't see that there would
9 bias in deciding to not take the test per se.
10 DR. GREEN: Mark Green. I voted no. I
11 don't believe that these assessments give a full
12 and adequate assessment of the disabilities of the
13 condition.
14 DR. HOFFMAN: Richard Hoffman. I voted yes.
15 I think there was plenty of potential for bias but
16 no real evidence of any bias, so we really don't
17 know. And I would say that it's just speculation
18 that there was.
19 DR. ALEXANDER: Thank you very much. Those
20 are very helpful comments.
21 So there were comments regarding the fact
22 that this was open label and the panelists would

1 have loved to have seen a blinded adjudication of
2 outcome. There were concerns regarding the fact
3 that some control patients were deemed unable to do
4 a 6-minute walk test and concerns regarding whether
5 or not they were truly unable to do so.
6 Another panelist felt there were no concerns
7 about motivation for the boys and more concern
8 about difficulty of using historical controls and
9 all of the biases that we cannot measure.
10 One panelist felt that there were concerns
11 about the question itself and had trouble knowing
12 how to interpret this to make a firm yes or no
13 answer.
14 The effect of historical controls is
15 unknowable, also concerns about the potential
16 motivational bias that may be present. More than
17 one panelist commented -- again, we're back to the
18 fact that there was a 6-minute walk time or no
19 6-minute walk time for a few subjects that had
20 10-meter data present, and so panelists questioned
21 the objectivity and comparability of the 6-minute
22 walk test.

1 One felt a predetermined selection criteria
2 were not sufficient to control for biases as open
3 label. One wavered between yes and abstain but
4 didn't believe that patients were extra motivated
5 to maintain mobility, that is that they're
6 sufficiently motivated and thus less of a concern
7 regarding motivational bias.
8 One felt that there were concern that we're
9 losing grasp with heterogeneity of disease
10 progression, and they felt that it isn't
11 appropriate to analyze the data based on patient's
12 age, and felt that it was more appropriate to
13 analyze based on children's stage of development.
14 One was disappointed with the data that was
15 analyzed and felt that patients weren't randomized
16 and wasn't convinced that historical controls were
17 comparable, but the real problems is the endpoint
18 itself. It doesn't look at upper body; it only
19 looks at lower body. There are better measures
20 such as for ALS.
21 One felt there was a differential and
22 believes the FDA should require non-ambulatory arms

1 in every DMD trial, lots of things to be studied.
2 Another voted yes because the 6-minute walk
3 test was felt to be sufficient. And given how much
4 patients with DMD want to continue walk, the
5 panelist didn't see how there could bias in terms
6 of not taking the test.
7 One felt that the assessments didn't provide
8 a full and adequate assessment of the condition.
9 And the final panelist mentioned as support for
10 their vote that, yes, that they didn't believe that
11 there was any real evidence of any bias.
12 So we'll move on to the next question. So
13 I'll read the question, but I also want to provide
14 the panelists a chance to ask clarifying questions
15 of the FDA prior to the vote.
16 So the question is, question number 5, What
17 is the impact of the North Star Ambulatory
18 Assessment Results on the persuasiveness of the
19 findings in study 201/202?
20 Does the NSAA, the North Star Ambulatory
21 Assessment Results, does the NSAA strengthen the
22 persuasiveness of the findings in study 201/202?

1 Does it weaken the persuasiveness of the findings
2 or is there no effect?
3 So are there any clarifying questions on the
4 part of the panelists for the FDA regarding the
5 wording of this question and its meaning?
6 Yes, Dr. Gonzales?
7 DR. GONZALES: Nicole Gonzales. Are we
8 supposed to use of all of the data presented by
9 both Sarepta and the FDA or use one or the other?
10 DR. ALEXANDER: I think you'd be using the
11 totality of evidence that's been discussed and
12 presented today and provided in the briefing packet
13 to you.
14 Dr. Gordon?
15 DR. GORDON: The sponsor is asking for
16 permission to clarify something for the record
17 regarding the 6-minute walk test.
18 DR. ALEXANDER: If there is a specific
19 question on the part of a panelist seeking
20 clarification, then we can pursue that. But if
21 not, I'd like to proceed with this vote unless
22 there are questions of clarification for the FDA

1 regarding the wording of question 5.
2 Yes, Dr. Nuckolls?
3 DR. NUCKOLLS: So not regarding the wording,
4 but I see on slide, whatever, 85, 86, the
5 comparison of the slope of North Star in the
6 treated and control, and the standard deviation
7 error bars look like they're completely
8 overlapping. But I'm wondering is there any
9 evidence of a statistically significant difference
10 between --
11 DR. BASTINGS: The answer is no.
12 DR. ALEXANDER: Are there any further
13 questions of clarification for the FDA regarding
14 the wording of question 5?
15 (No response.)
16 DR. ALEXANDER: If not, we'll proceed to
17 vote.
18 So once again, what is the impact of the
19 North Star Ambulatory Assessment Results on the
20 persuasiveness of the findings in study 201/202?
21 Do these results, A) strengthen -- I'm sorry. I
22 guess it is A, B and C.

1 So do these results, A, strengthen the
2 persuasiveness; B) weaken the persuasiveness; or
3 C) no effect?
4 (Vote taken.)
5 DR. CHOI: Everyone has voted. The vote is
6 now complete.
7 DR. ALEXANDER: Thank you. So why don't we
8 begin with the first --
9 DR. CHOI: For the record, we have 2 votes
10 for A, strengthen; 5 votes for B, weaken; and
11 6 votes for C) no effect.
12 DR. ALEXANDER: Thank you. So we'll begin
13 with the first voting member on this side, and
14 please state your name, your vote, and a very brief
15 explanation of why you voted as you did.
16 DR. HOFFMAN: Richard Hoffman, and I voted
17 no effect, C, basically because there was a
18 complete difference of opinion on this matter
19 between the sponsor and the FDA. And it's kind of
20 who do you believe and how do you interpret the
21 data.
22 DR. ALEXANDER: Please continue.

1 DR. GREEN: Yes. Mark Green. Mine also is
2 an error. I wanted C as well. Please change my
3 vote because I don't think it had any persuasive
4 evidence either direction.
5 DR. ALEXANDER: Okay. So for the record,
6 Dr. Green is voting C, that it had no effect.
7 MR. DUPREE: Benjamin Dupree. I voted C. I
8 just don't see one way or the other that it
9 influences the persuasiveness.
10 MS. GUNVALSON: I'm Cheri Gunvalson. I
11 voted A. I felt the sponsor had a strong point.
12 DR. ALEXANDER: Can you just specify the
13 basis for that?
14 MS. GUNVALSON: Well, when Dr. McDonald
15 explained the findings, as others have said, there
16 are two sets of data. I mean, I wavered between C
17 and A, but that's where I'm at.
18 DR. KRYSCIO: Richard Kryscio. I voted on
19 the weakened side because of the graph I saw
20 produced by the FDA, two parallel lines, one line
21 below the other, indicating that that the
22 historical control group was not comparable.

1 It helped convince me the historical control
2 group is not comparable to the randomized patients.
3 And there's a large variability in there showing no
4 statistical difference between the two parallel
5 lines. And finally, that has to do with the sample
6 size that was chosen, I'm sure. And this
7 measurement, NSAA, is closer to a functional rating
8 scale than is the 6-minute walk test.
9 DR. ROMITTI: Paul Romitti. I voted C, no
10 effect and for reasons discussed.
11 DR. NUCKOLLS: Glen Nuckolls. I voted B,
12 weakened. So the North Star test measures function
13 of many of the same muscle groups as the 6-minute
14 walk. And since there is no statistically
15 significant difference between the treated and
16 control groups, that in my mind weakens the
17 strength of the 6-minute walk data.
18 DR. FOLEY: Reghan Foley. I voted C, no
19 effect. For me, it didn't lessen or weaken or
20 strength the results. For me, the main issue to
21 preserve ambulation.
22 DR. KESSELHEIM: Aaron Kesselheim. I voted

1 C, no effect. I was also moved by the slides with
2 the really, really large error bars, again,
3 indicating probably just the small numbers of
4 patients in this comparison.
5 But, these are all sort of historical
6 control comparisons performed after the trial had
7 already sort of been started and going along, so
8 some of them might turn out positive; some of them
9 negative. And for me, this ended up being one of
10 the many different things that were tested, and
11 therefore, to me, overall had no effect.
12 DR. ALEXANDER: Caleb Alexander. I felt
13 that it weakened the evidence that was presented
14 primarily because the NCAA, as I understand it,
15 assesses -- is comprised of many more measures than
16 a single dimensionality. So I guess that leads me
17 to feel a little bit more confident in it as an
18 overall assessment.
19 There was also a difference at baseline,
20 which I guess raised concerns for me about the
21 comparability of the two groups at baseline. But
22 the trajectories, the trend lines are virtually

1 indistinguishable, and the confidence intervals
2 overlap.
3 So for me, I think I would have been more
4 convinced about the evidence in 201 and 202 even
5 though those studies, the primary endpoints, as I
6 understood them, were not achieved. I would have
7 been more confident about the longer term follow-up
8 data that was presented and the open label had the
9 NSAA been more compelling.
10 DR. ONYIKE: Chiadi Onyike. I voted no. As
11 already mentioned, the NSAA is a more comprehensive
12 measure than the 6-minute walk test or the
13 10-minute test. But in any case, neither the FDA,
14 nor the sponsor is claiming a statistically
15 significant difference between the groups on this
16 measure.
17 DR. GONZALES: Nicole Gonzales. I voted no
18 for reasons already mentioned.
19 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
20 for reasons already mentioned.
21 DR. ALEXANDER: Okay. Thank you very much.
22 So for those that voted no effect primarily felt

1 that they didn't see that this influenced things
2 one way or another.
3 They were moved by -- one was moved -- one
4 panelist mentioned being influenced by the slides
5 with the large error bars, probably indicating
6 small numbers of patients within the comparisons.
7 These are all historical comparisons
8 performed after the trial had been started as some
9 might turn out to be positive, some negative. But
10 it turned out as one of many things that were
11 tested.
12 Those that felt that the NSAA data
13 strengthened the results of studies 201 and 202
14 felt that the sponsor had a strong point. One
15 panelist mentioned having wavered between no effect
16 and strengthens.
17 Those that felt that the data weakened the
18 results of the 201 and 202 felt that there were two
19 parallel lines; one was lower than the other. This
20 helped convinced one panelist that the historical
21 control was not comparable.
22 The results of large variability, no

1 statistically significant difference, large
2 variation was felt partly due to sample size. NSAA
3 was felt to be closer to a functional rating scale
4 than the 6-minute walk test. It measures function
5 of many of the muscle groups as a 6-minute walk
6 test, so since no difference, this was felt to
7 weaken the association.
8 It was also pointed out that this was a more
9 comprehensive measure and that neither the FDA or
10 the sponsor is claiming that there was a
11 significant difference between groups on this
12 measure.
13 So thank you very much for that. And moving
14 right along, we'll move to question 6, which is,
15 what is the impact of the other tests of physical
16 performance such as rise time, 10-meter run/walk on
17 the persuasiveness of findings in study 201/202?
18 So a very similar question, but in this
19 case, we're discussing not the North Star
20 Ambulatory Assessment but the other test of
21 physical performance: rise time and 10-meter
22 run/walk as two examples of those.

1 Are there any questions clarifying this
2 question for the FDA; that is, do the panelists
3 have any questions for the FDA about what's being
4 asked?
5 (No response.)
6 DR. ALEXANDER: Okay. Very good. So we'll
7 move to voting then. Once again, the question is,
8 What is the impact of the other test of physical
9 performance such as rise time or 10-meter run/walk
10 on the persuasiveness of findings in study 201 and
11 202?
12 Does it strengthen the persuasiveness of the
13 findings, does it weaken the persuasiveness of the
14 findings, or is there no effect?
15 (Vote taken.)
16 DR. CHOI: Everyone has voted. The vote is
17 now complete. For the record, we have 1 vote for
18 A, strengthen; 2 votes for B, weaken; 10 votes for
19 C, no effect.
20 DR. ALEXANDER: Thank you. So why don't we
21 begin with Dr. Hoffman? If you could state your
22 name, and your vote and a brief justification or

1 explanation of why you voted as you did for the
2 record.
3 DR. HOFFMAN: Richard Hoffman. And I voted
4 C, no effect because of the same reasons from the
5 previous question.
6 DR. ALEXANDER: And those reasons were?
7 DR. HOFFMAN: Well, in my opinion, there
8 were differences of opinion between the FDA and the
9 sponsor. And I really didn't think one or the
10 other proved the case one way or the other for that
11 particular testing.
12 DR. ALEXANDER: Thank you. Dr. Green?
13 DR. GREEN: Yes. I voted C too because I
14 think these represent too small of a sampling error
15 to be convincing about the disability caused by the
16 condition.
17 DR. ALEXANDER: Just so I understand you
18 that they represented too small a sampling error?
19 DR. GREEN: Sampling the -- there's a lot of
20 overlap between the muscles involved in those two
21 tests, so I think they don't represent the totality
22 of the muscle disorder.

1 DR. ALEXANDER: Thank you. Mr. Dupree?
2 MR. DUPREE: Benjamin Dupree. I voted C, no
3 effect. I don't really see that these influence
4 persuasiveness one way or the other because, based
5 on the testimony, it seems like -- I can't see a
6 real correlation between these and the 6-minute
7 walk test.
8 MS. GUNVALSON: Cheri Gunvalson. I voted A.
9 I believe Dr. McDonald gave a good presentation on
10 how rise time affects ability to walk, and I
11 thought it strengthened it.
12 DR. KRYSCIO: Richard Kryscio. I voted no
13 effect. These, I viewed as secondary outcomes and
14 it didn't factor into my opinions on this. And
15 there was certainly disagreement between sponsor
16 and the FDA.
17 DR. ROMITTI: Paul Romitti. I voted C, no
18 effect for the same reasons just explained.
19 There's agreement on how to handle rise time
20 between the FDA and the sponsor. And also,
21 10-meter walk run, I don't think really adds much
22 to the outcome assessment here.

1 DR. NUCKOLLS: Glen Nuckolls. I voted no
2 effect. So I get Craig McDonald's point that its
3 ability to rise and not time to rise, but that's
4 just one component of the North Star. But I give
5 that kind of a little bit of strengthen. And then
6 the data from the FDA, it showed there's really no
7 difference in 10-meter walk with the other way, so
8 they kind of cancelled out.
9 DR. FOLEY: Reghan Foley. I voted C, no
10 effect for reasons already stated. These are
11 secondary outcomes. It didn't really strengthen or
12 weaken the results, in my eyes.
13 DR. KESSELHEIM: Aaron Kesselheim. I also
14 voted no effect because the secondary outcomes
15 didn't clearly show evidence one way or other. And
16 given the very small sample size, I don't think
17 that there is much that they add one way or other
18 on the main question.
19 DR. ALEXANDER: Caleb Alexander. I felt
20 that they weakened the results or conclusions one
21 reaches about studies 201/202 primarily because I
22 think the -- in this type of setting where there's

1 questions about the adequacy of the historical
2 controls and the -- I mean, the amount of
3 dystrophin produced, the adequacy of the historical
4 controls and the relationship between the
5 dystrophin production and outcomes assessed, I
6 would have liked to have seen more convincing
7 evidence of the effect of the study drug on these
8 outcomes.
9 I think in particular, looking at the
10 experience of individuals over time by age
11 influenced me to feel that these weaken the
12 findings.
13 DR. ONYIKE: Chiadi Onyike. I voted weaken
14 as well for the reasons -- firstly, for the reasons
15 that Dr. Alexander has explained. But also taking
16 into account Dr. McDonald's explanation, I think
17 that at the end of the day, you still have to
18 control for either age at baseline or age at
19 illness onset if you wish to account for illness
20 duration.
21 I don't think that you can look at these
22 time-dependent measures independent of some

1 adjustment for age. And unfortunately, the sample
2 is not large enough to successfully do that. But I
3 think anyone would agree that in a large enough
4 sample, you would be remiss not to control for age.
5 DR. GONZALES: Nicole Gonzales. I voted no
6 effect. In the absence of a concurrent control
7 group, it makes it very difficult for me to
8 interpret the results of any of the secondary
9 outcome measures.
10 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
11 effect even though I thought it slightly diminished
12 the effect. But I think there's enough conflict
13 about the interpretation of how to look at this
14 that I thought on balance overall, the effect, if
15 anything, was very minimal.
16 DR. ALEXANDER: Okay. So those that felt
17 that it strengthened the association felt that rise
18 time affects the ability to walk and that there was
19 a good rationale for why these might be linked.
20 Panelists that felt that this weakens the
21 persuasiveness of the associations, I should say in
22 studies 201/202, felt that a collateral information

1 is very important, especially in this setting where
2 questions have been raised about the primary
3 endpoints and the 6-minute walk test results.
4 There was a comment that at the end of the
5 day, you have to control for age at baseline or
6 illness onset and that one can't look at these
7 measures without adjustment for age. But the
8 sample isn't large enough to do so, that is to
9 adjust for age.
10 Then, for those that felt there was no
11 effect, reasons to support that included that there
12 are differences in opinion between the FDA and the
13 sponsor. Neither proved a case one way or the
14 other for that particular testing. A lot of muscle
15 is involved between these two tests so that they
16 don't represent the totality of muscles involved in
17 this disorder.
18 Panelists felt that they don't see that
19 these tests influence the persuasiveness one way or
20 the other, that there was disagreement with how to
21 handle the rise time between the FDA and the
22 sponsor, that the 10-meter test doesn't add much to

1 the outcome.

2 Another panelist made the point that they

3 get the point that it's the ability to rise, not

4 time to rise that give some strength in the data

5 that was provided by the FDA.

6 Panelists felt that these are secondary

7 outcomes and therefore didn't strengthen or

8 weakened the associations -- or the persuasiveness

9 of the findings of studies 201/202, that the

10 evidence regarding these outcomes didn't clearly

11 show evidence one way or another; that there was a

12 small sample size that didn't add much; that in the

13 absence of a concurrent control group, difficult to

14 interpret any of these secondary outcome measures.

15 So those were some of the rationales for

16 those panelists that felt that there was no effect

17 here.

18 The last question is a voting question,

19 which is whether or not the clinical results of the

20 single historically-controlled study, that is

21 study 201/202 provide substantial evidence, i.e.,

22 evidence from adequate and well-controlled studies

1 or evidence from a single highly persuasive,
2 adequate and well-controlled study that is
3 accompanied by independent findings, that
4 substantiate efficacy that eteplirsen is effective
5 for the treatment of DMD.
6 So here again, are there questions to
7 clarify this for the FDA?
8 (No response.)
9 DR. ALEXANDER: Are there clarifying
10 questions on the part of the panelist?
11 (No response.)
12 DR. ALEXANDER: If not, then we'll move to
13 voting. Once again, the question is, do the
14 clinical results of the single historically-
15 controlled study, study 201 -- I'm sorry. There's
16 a question? Yes?
17 DR. ONYIKE: Yes. Forgive me.
18 DR. ALEXANDER: Can you identify yourself
19 please?
20 DR. ONYIKE: My name is Chiadi Onyike. To
21 what extent are we to incorporate into this
22 question the testimony of the families, the boys

1 and their families?
2 (Applause.)
3 DR. ONYIKE: From my reading of the
4 question, it would seem narrowly worded towards the
5 actual statistical results. So I just want some
6 clarification on that point.
7 DR. ALEXANDER: Can the FDA address that
8 question, please?
9 DR. WOODCOCK: Well, we are instructed, as
10 people said, to take the use of the patient
11 community into account, more on the benefit and the
12 risk.
13 (Applause.)
14 DR. WOODCOCK: So the statutory standard is
15 more or less as described there, but there is
16 flexibility, and that's where we should take the
17 views of the community into account.
18 DR. ONYIKE: Sorry. If I might just follow
19 on. So if I understand you correctly, this
20 question, as worded, is really about statistics; is
21 that correct?
22 DR. ALEXANDER: Would it be fair to suggest

1 that you should take into account the totality of
2 information in the briefing packet and what's been
3 discussed today?
4 DR. WOODCOCK: I think that's fair. The
5 standard is adequate and well-controlled trials.
6 That's what's in the statute. But we are
7 instructed to have flexibility in how we interpret
8 that based on the medical need. So I think,
9 Dr. Alexander, that's a fair summation.
10 Bob wants to say something.
11 DR. TEMPLE: There are lots of questions
12 raised about the study, whether there was improper
13 influence of the fact that people knew what the
14 study was and all that kind of stuff.
15 You heard testimony from patients who said
16 very explicitly that they didn't think that would
17 alter the level of effort that people made. So
18 those kinds of factors are certainly things that
19 are up for discussion.
20 You know, whether it's persuasive or not,
21 whether the study is persuasive enough, that has a
22 lot to do with the study design and what was

1 measured, size of the treatment effect and all
2 those things. But you heard testimony that might
3 affect your views on the quality of the endpoints,
4 on the importance of lack of blinding, and all
5 kinds of stuff like that.
6 DR. ALEXANDER: Dr. Unger?
7 DR. UNGER: I think with the majority of the
8 patients here, we have an incredible advantage that
9 we -- I mean, in my time with the FDA, it's
10 unprecedented to have basically all of the patients
11 here. So that's an important advantage that we
12 have.
13 One of the things that you can do is try to
14 reconcile what you've heard from the patients with
15 the data that you've seen presented by the company.
16 We're hearing patients are improving, doing things
17 next year that they didn't do last year. And you
18 have to figure out if you can reconcile that with
19 the actual hard data that you've been analyzing
20 today.
21 DR. ALEXANDER: Yes? Please state your name
22 and question for the record for the FDA clarifying

1 this question.
2 DR. ROMITTI: Paul Romitti. This is
3 directed to Dr. Woodcock because when I look at
4 this question and I think of the first one we
5 discussed, you're talking about two
6 different -- there are some overlap in subjects,
7 but you're talking about two different groups,
8 particularly with the controls.
9 So I want to understand if we are to
10 consider the dystrophin results, which were tested
11 on some different people than in the one or two, or
12 we just talking about the other part of the study?
13 DR. WOODCOCK: This is the full approval
14 question, and that is based on the empirical
15 results in the clinic. I agree with what Dr. Unger
16 said. They're not based on the persuasiveness of a
17 surrogate endpoint. They're based on the
18 persuasiveness of the trial that was done.
19 DR. ALEXANDER: Thank you. One more
20 question of clarification. Please state your name
21 for the record.
22 DR. OVBIAGELE: Bruce Ovbiagele. Because I

1 would have two different answers to the questions.
2 One would be objective; one would be subjective.
3 And it's how to reconcile both in the same question
4 here that I guess is the issue.
5 DR. ONYIKE: This is Chiadi Onyike. If I
6 may quickly add to that, the question twice
7 mentions "well controlled," and as you've heard
8 repeatedly, people have said that they have trouble
9 the control. So this "well controlled" phrase, in
10 a sense, tips or constrains the question.
11 DR. TEMPLE: I understand a lot of people
12 don't like historically-controlled trials. They're
13 not sure they believe they're well controlled. Our
14 regulations since 1970 have said that a
15 historical-controlled trial can be a
16 well-controlled study, an adequate and
17 well-controlled study.
18 The question here goes to, do you think,
19 under the circumstances, that it was? Do you think
20 the way they selected them was right? Do you think
21 the way analyzed them was right; good enough to
22 make it an adequate and well-controlled study?

1 That's the question.
2 DR. DUNN: Yes --
3 DR. TEMPLE: Historically-controlled trials
4 have been the basis for approval, sometimes in sort
5 of obvious cases; sometimes in cases that aren't
6 quite as obvious.
7 DR. DUNN: Yes. Billy Dunn. I want to
8 reiterate all of these issues. I think it's very
9 important to take into account the testimony you
10 heard here today because you heard half of the
11 comparison. You heard from the patients in the
12 201/202 trials.
13 They're being compared to a historical
14 control. One of the reasons that I opened up the
15 meeting, and many others reiterated the issues that
16 I abruptly spent so much time talking about what
17 substantial evidence is and what adequate and
18 well-controlled studies are, so that you can sort
19 out whether or not the evidence provided from this
20 study, with the information that you have at hand
21 here from the patients as well as what's provided
22 by the -- what you referred to as more objective

1 results, rises to the standard that it creates
2 substantial evidence of effectiveness, which again
3 most traditionally is provided by two adequate and
4 well-controlled trials.
5 We did not set out to refute the notion that
6 the historical control was unacceptable by design.
7 I think we took pains to actually illustrate that
8 that was potentially acceptable.
9 What we've done is describe to you the
10 concerns that the team had that have to do with the
11 comparability of that control, the acceptability of
12 the use of that control.
13 So the issue here is that substantial
14 evidence question of whether or not in comparison
15 with the group, with all the issues that we've
16 heard and everything you've heard today, it serves
17 to reach that level of evidence.
18 DR. ALEXANDER: Thank you. Are there any
19 other final questions clarifying this question
20 before we move to voting?
21 (No response.)
22 DR. ALEXANDER: Okay. So we'll move to

1 voting then, and I'll read the question. If you've
2 voted once, please do so again. And the question
3 is as follows:
4 Do the clinical results of the single
5 historically-controlled study, study 201/202,
6 provide substantial evidence, that is evidence from
7 adequate and well-controlled studies or evidence
8 from a single highly persuasive adequate and
9 well-controlled study that is accompanied by
10 independent findings that substantiate efficacy,
11 that eteplirsen is effective for the treatment of
12 DMD?
13 (Vote taken.)
14 DR. CHOI: Everyone has voted. The vote is
15 now complete. We have 3 yes, 7 no, 3 abstentions.
16 DR. ALEXANDER: Thank you. Why don't we
17 begin with Dr. Hoffman? If you can state your name
18 and your vote for the record and a brief
19 explanation of why you voted as you did.
20 DR. HOFFMAN: Richard Hoffman. And I voted
21 to abstain and the reason was, is I was basically
22 just torn between my mind and my heart. And I

1 don't want to make type 1 error, and I don't make a
2 type 2 error.
3 DR. ALEXANDER: Thank you. Dr. Green?
4 DR. GREEN: Mark Green. I also abstained
5 because I'm uncomfortable by the language of the
6 question because I think it's a bit leading even
7 though I recognize that's the answer that's
8 requested of us, because I don't believe that an
9 external control is customary in a study like this
10 at all, so I can't say I'm in favor of that.
11 But I'm very fearful that we'll leave here
12 with some sort of stalemate between the FDA and the
13 panel, where I'm still quite sympathetic and
14 persuaded by the public's presentations.
15 MR. DUPREE: Benjamin Dupree. I voted yes
16 because I can't really reconcile the difference
17 between the testimony that was given suggesting
18 that the boys' recovering abilities, I
19 don't -- living with Duchenne, I don't understand
20 how that's even possible.
21 But at the same time, this study doesn't
22 prove from a -- like it doesn't provide what I

1 think is adequate evidence to support all this
2 testimony that I'm seeing and hearing.
3 MS. GUNVALSON: Cheri Gunvalson. I voted
4 yes. I believe there's substantial evidence in
5 supporting this.
6 (Applause.)
7 DR. KRYSCIO: Richard Kryscio. I voted no.
8 It's not a well-controlled study. I was not
9 convinced that the data was there to basically
10 approve something on the basis of one poorly
11 controlled trial.
12 DR. ROMITTI: Paul Romitti. I voted to
13 abstain. Like the other panelists before me, I was
14 conflicted with this vote because I do see
15 limitations. And as a scientist, I cannot say that
16 this study -- and answer the question as
17 written -- was adequate and well controlled for a
18 number of reasons.
19 But I also was moved by the testimony, the
20 public testimony as well. And I'm also concerned
21 that we keep getting more and more information
22 about why there wasn't a placebo-controlled trial.

1 I'd asked for clarification earlier on in
2 the meeting about when Sarepta was told or asked to
3 do a placebo-controlled trial and received a date
4 of several years ago. And I'm surprised
5 that -- and I feel like maybe that they needed to
6 consider that. Now, we hear maybe they didn't have
7 enough drug.
8 So more information keeps coming out, so I'm
9 uncomfortable -- as much as I'd like to say yes,
10 I'm uncomfortable with the evidence to date to say
11 yes. I'm moved by the public testimony, but I'm
12 not as uncomfortable to just say no. I think
13 there's still room to work here.
14 DR. NUCKOLLS: Glen Nuckolls. I voted no.
15 I thought that there were significant concerns
16 regarding the ability to draw valid conclusions
17 from this design of an externally-controlled
18 comparison.
19 DR. FOLEY: Reghan Foley. I voted yes. As
20 a pediatric neuromuscular specialist, for me,
21 there's substantial evidence that there's
22 amelioration of the clinical phenotype of Duchenne

1 dystrophy. I believe that more data is needed, and
2 I also believe that looking at other biomarkers, as
3 Professor Partridge pointed out, would very helpful
4 as well. But I did feel that the phenotype was
5 clearly ameliorated.
6 DR. KESSELHEIM: Aaron Kesselheim. I voted
7 no. I felt like a historically-controlled study
8 could provide substantial evidence, but this one
9 did not both in its results and its design. I felt
10 like it could therefore be used potentially as
11 supportive. But the original controlled study,
12 placebo-controlled study, the 12 patients was
13 negative. So if it was going to be supportive or
14 secondary, it was going to be secondary to
15 something that did not show an effect.
16 Then I was also confused -- I was also
17 confused a little bit by the fact that there did
18 appear to be evidence from the audience from more
19 patients that were presented here from some of
20 these newer studies and some of these extension
21 studies.
22 So I think that there is still information

1 to learn about this drug. But as the data
2 currently stand, it doesn't appear to me that this
3 historically-controlled study provides substantial
4 evidence.
5 DR. ALEXANDER: Caleb Alexander. I voted
6 no. I just felt that this wasn't a well-controlled
7 study and that the ways that the controls were
8 selected and analyzed didn't meet the threshold
9 that I would consider to be adequate and well
10 controlled.
11 We heard criteria for what constitutes a
12 well-controlled study. And even if the study was
13 well controlled, I have concerns regarding the
14 conclusions reached about the efficacy of
15 eteplirsen.
16 DR. ONYIKE: Chiadi Onyike. I voted no.
17 Basically, the findings do not support a conclusion
18 of yes, at least on the statistical grounds and
19 scientific grounds. And unfortunately, what I
20 would consider meaningful evidence or testimony
21 from the families is not properly measured in the
22 study.

1 So I hope that in the future that the field
2 will incorporate measures of function. Someone
3 alluded to ALS fields. There are other fields.
4 I work also in the dementia field where
5 caregiver outcomes are routinely included in the
6 clinical trials. I think there needs to be a move
7 in that direction so what you report are not
8 considered soft outcomes. I also hope you would
9 consider, as a community, participating fully in
10 controlled trials so that you're not in this
11 position in the future.
12 (Audience interrupts.)
13 DR. ALEXANDER: I'm sorry, please. We have
14 to continue with the explanation.
15 DR. ONYIKE: My apologies. I don't mean --
16 (Audience interrupts.)
17 DR. ALEXANDER: I'm sorry. The audience --
18 DR. ONYIKE: Let me speak to that, please.
19 DR. ALEXANDER: No, actually, I'd like to
20 move on.
21 DR. ONYIKE: Let me speak to it. I made the
22 comment, please. Please.

1 DR. ALEXANDER: No.
2 (Audience interrupts.)
3 DR. ONYIKE: I'm sorry. I didn't mean to be
4 critical or lecturing. What I meant to say -- what
5 I meant to address was the --
6 DR. ALEXANDER: Thank you. May we have
7 the -- Dr. Gonzales?
8 DR. GONZALES: Nicole Gonzales. I voted no.
9 The placebo portion of the study wasn't positive on
10 the primary outcome measures, and I had issues with
11 the historical control for secondary clinical
12 endpoints.
13 DR. OVBIAGELE: Bruce Ovbiagele. I voted
14 no. I thought it wasn't a well-controlled study at
15 all. If I had to vote based on the testimony I
16 heard, if this was a before and after question,
17 definitely based on all that I heard, the drug
18 definitely works, but the question was framed
19 differently.
20 DR. ALEXANDER: Thank you. So I'd like to
21 just for the record summarize the comments that
22 I've heard.

1 (Audience interrupts.)
2 DR. ALEXANDER: I'd like to try to get this
3 entered in to the record and not adjourn the
4 meeting prematurely. So out of respect for all of
5 the individuals that are here, I request that you
6 allow for me to summarize briefly the comments that
7 we've heard thus far.
8 So those that voted yes felt that one
9 couldn't reconcile the differences between
10 testimony that was given suggesting boys were
11 recovering abilities, didn't understand how that
12 was possible, but the study didn't provide what was
13 felt to be adequate evidence to support all of this
14 testimony that the panelists were seeing.
15 They felt that there was substantial
16 evidence that the phenotype clearly improved, but
17 there was an encouragement for the collection of
18 more data, including biomarkers.
19 Individuals that voted no felt that it was
20 not a well-controlled study, that the data wasn't
21 there to approve something on the basis of one
22 poorly controlled trial. There were significant

1 concerns raised about the ability to draw valid
2 conclusions from this type of external comparison.
3 One panelist commented that the historical
4 control could provide sufficient information but
5 that this one did not and was also confused by the
6 fact there appear to be evidence from newer studies
7 or extension studies. And the panelist felt that
8 more information would be helpful to learn about
9 this product.
10 One felt that there wasn't -- that this
11 wasn't a well-controlled study, so here again that
12 the ways the controls were selected and analyzed
13 didn't meet the threshold that they felt would
14 constitute to be adequate and well controlled.
15 We heard criteria for what constitutes a
16 well-controlled study. A panelist commented that
17 even if it was well controlled, that there was
18 reason to question the conclusions regarding
19 efficacy that were reached.
20 A panelist commented that based on
21 scientific and statistical grounds, what they would
22 consider meaningful testimony from the families was

1 not optimally assessed in the study and that
2 caregiver outcomes are routinely included in
3 randomized trials in dementia, and that this might
4 be pursued in DMD. And one panelist also commented
5 that the placebo portion of the study was not
6 positive on outcome measures.
7 Those that abstained, one panelist felt that
8 he was torn between his mind and his heart. He
9 doesn't want to make a type 1 error but doesn't
10 want to make a type 2 error either.
11 One panelist was uncomfortable by the
12 language of the question and felt that it was a
13 little leading and didn't feel that external
14 control is -- that having an external control is
15 customary, wouldn't favor that; but one panelist
16 noted that they feared that we would leave with a
17 stalemate between the FDA, and they said the panel,
18 but I imagine they meant the sponsor, maybe not.
19 One panelist noted that they do see
20 limitations, that they didn't feel that they could
21 answer the question affirmatively, but they were
22 also moved by the public testimony and also

1 concerned that more and more information -- they
2 were concerned with the additional information
3 about why there wasn't a placebo-controlled trial
4 and that they had asked for that information early
5 in the meeting and then told that the date was, I
6 believe, in 2011 that Sarepta was encouraged to
7 pursue an RCT. That panelist felt uncomfortable
8 with evidence to-date to say yes but they were
9 moved by the public testimony.
10 Before we adjourn, I would like to give the
11 opportunity to the FDA, if there are any final
12 comments from the FDA?
13 DR. DUNN: Billy Dunn, FDA. The emotion and
14 passion in the room during the discussion is clear.
15 And I mentioned at the beginning of the day that we
16 listen and we listen carefully. And although I
17 recognize there's great concern about the
18 discussion and the results of the votes, I assure
19 you that we listened very carefully.
20 We've heard some very meaningful testimonies
21 today, and we've observed the panel be highly
22 influenced by that testimony. I assure you that we

1 will take the information we've learned here today
2 under very serious consideration as we adjourn this
3 meeting.

4 **Adjournment**

5 DR. ALEXANDER: Thank you. And I'd just
6 like to add my thank you to the patients and
7 friends and family, the members of the general
8 public. Many of you exerted a tremendous effort to
9 get here, and I appreciate your participation.
10 Also, I'd like to thank the FDA staff and
11 scientists, the sponsor for the enormous amount of
12 work that all of you and your colleagues have
13 performed in order to make today possible. I'd
14 also like to thank the conference center staff as
15 well for helping to host this event.
16 Once again, thank you for your contribution
17 to today's meeting. The meeting is now adjourned.
18 Panel members, please take all your personal
19 belongings with you as the room is cleaned at the
20 end of the meeting today. All materials left on
21 the table will be disposed of.
22 Please also remember to drop off your name

1 badge at the registration table on your way out so
2 that they may be recycled. Thank you again for
3 your participation.
4 (Whereupon, at 7:37 p.m., the meeting was
5 adjourned.)
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