Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
April 25, 2016

Location: College Park Marriott Hotel and Conference Center, Chesapeake Ballroom
3501 University Blvd. East, Hyattsville, MD 20783

Topic: The committee discussed new drug application (NDA) 206488, eteplirsen injection for intravenous infusion, sponsored by Sarepta Therapeutics, Inc., for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

These summary minutes for the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on July 5, 2016.

I certify that I attended the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	G. Caleb Alexander, MD, MS
Designated Federal Officer, PCNS	Chairperson, PCNS

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
April 25, 2016

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on April 25, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm478063.htm.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 25, 2016, at the College Park Marriott Hotel and Conference Center, Chesapeake Ballroom, 3501 University Blvd. East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Sarepta Therapeutics, Inc. The meeting was called to order by G. Caleb Alexander, MD, MS (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 500 people in attendance. There were 52 Open Public Hearing (OPH) presentations.

Issue: The committee discussed new drug application (NDA) 206488, eteplirsen injection for intravenous infusion, sponsored by Sarepta Therapeutics, Inc., for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): G. Caleb Alexander, MD, MS (Chairperson); Nicole R. Gonzales, MD; Mark W. Green, MD, FAAN; Richard P. Hoffman, PharmD; Chiadi U. Onyike, MD; Bruce I. Ovbiagele, MD, MSc, MAS

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Merit Cudkowicz, MD; Joel S. Perlmutter, MD

Peripheral and Central Nervous System Drugs Advisory Committee Member Present (Non-Voting): Mark Gordon, MD

Temporary Members (Voting): Benjamin Dupree (Patient Representative); A. Reghan Foley, MD; Cheri Gunvalson, RN, MS (Patient Representative); Aaron S. Kesselheim, MD, JD, MPH; Richard J. Kryscio, PhD; Glen Nuckolls, PhD; Paul Romitti, PhD

FDA Participants (Non-Voting): Janet Woodcock, MD; John Jenkins, MD; Ellis Unger, MD; Robert Temple, MD; Billy Dunn, MD; Eric Bastings, MD; Ronald Farkas, MD, PhD

Open Public Hearing Speakers: Congressman Michael Fitzpatrick; Karen Jurack; Carlo Basile (Massachusetts Governor's Office); Malanie Miner; Christine McSherry, RN (Jett Foundation); Brady and Martha Williams; Kris Paschal, Chris Dunne, Denise Taborski and Sadie Anderson; Sue Fletcher, PhD (Centre for Comparative Genomics at Murdoch University in Perth, Western Australia); Barry J. Byrne, MD, PhD; Laura Gottschalk (National Center for Health Research); Linda Lowes, PT, PhD; Kathryn Wagner, MD, PhD; Jodi Nichols and Jenn Dumm (John Owen's Adventure, Inc.); Peter Heydemann, MD; Ann Connolly, MD; Austin Leclaire; Neera Gulati, MD; Manni Scarso, Louise Crow-Arnold and James Arnold; Cole and Kim Eichelberger; Billy and Terri Ellsworth; Debra Miller (Cure Duchenne); Jordan McSherry on behalf of Jett McSherry; Tracy Secker, Valerie Pappas Llauro, Amy Martin, Scott Griffin and Lisa Lee; Max Leclaire and Jenn McNary; Terence Partridge, PhD; Caden Bower and Beth Perez; M. Carrie Miceli, PhD; Susan Patterson and Wendy Kelly; Mitch Leffler; Keith Wesley; Ryan and Ana Vaish; Jack Willis, Nolan Willis, Alison Willis and Alec Hoke; Alex Smith (Harrison's Fund), Alex Johnson and Andrew Johnson (Joining Jack), Emily Crossley (The Duchenne Children's Fund), Lisa Kuhwald, Zoe Ward, Alasdair Robertson and Robyn Pete; Patricia Furlong (Parent Project Muscular Dystrophy); Brian Denger, Trina Stelly, Mel and John Kelly and Katy Pease; Stan Nelson, MD; Bill and Kim Procko; Marissa Penrod, Catherine Jayasuriya, Anessa Fehsenfeld, Dave Schultz, Kelly Maynard and Natalie Gaudenzi; Rose A. Juhasz, PhD; Perry Shieh, MD, PhD; Elizabeth McNally, PhD; Kadee Roden, Christina Burrell, Ethan Marquez, and Sandra Katzin; Jeff Chamberlain, PhD; Brian Wolf, Amy Aikins, Laura and Jeff McLinn, Chris Diemler and Cindy Quitzau; Lou Kunkel, PhD; Mindy Leffler; John Day, MD, PhD; Roger Lopez (International Association of Fire Fighters); Valerie Cwik, MD (Muscular Dystrophy Association); Chelsey Hickman on behalf of Shannon DeMatteo; Aidan Leffler; Laura McLinn on behalf of Senator Joe Donnelly

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**G. Caleb Alexander, MD, MS** Chairperson, PCNS
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Billy Dunn, MD** Director Division of Neurology Products (DNP), Office of Drug Evaluation I (ODE-I) Office of New Drugs (OND) CDER, FDA
APPLICANT PRESENTATIONS	**Sarepta Therapeutics, Inc.**
Introduction	**Shamim Ruff, MSc** Senior Vice President Regulatory Affairs and Quality Sarepta Therapeutics, Inc.

APPLICANT PRESENTATIONS (CONT.)

Disease Background and Natural History	**Eugenio Mercuri, MD, PhD** Professor of Pediatric Neurology Catholic University of the Sacred Heart
Efficacy	**Edward M. Kaye, MD** Chief Medical Officer (Interim CEO) Sarepta Therapeutics, Inc.
Safety	**Helen Eliopoulos, MD** Senior Medical Director Sarepta Therapeutics, Inc.
Clinical Perspective	**Jerry Mendell, MD** Director, Center for Gene Therapy Professor of Pediatrics and Neurology Curran-Peters Chair of Pediatric Research Nationwide Children's Hospital
Concluding Remarks	**Edward M. Kaye, MD**

APPLICANT GUEST SPEAKER PRESENTATION

Patient and Caregiver Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne	**Christine McSherry** Executive Director Jett Foundation
Clarifying Questions	

BREAK

FDA PRESENTATIONS

Center Director's Remarks	**Janet Woodcock, MD** Director CDER, FDA
Historically Controlled Trials	**Robert Temple, MD** Acting Deputy Director, ODE-I Deputy Center Director for Clinical Science CDER, FDA
FDA Efficacy Review	**Ashutosh Rao, PhD** Acting Chief Laboratory of Applied Biochemistry Division of Biotechnology Review & Research III Office of Biotechnology Products Office of Pharmaceutical Quality, CDER, FDA

FDA Efficacy Review (cont.)	**Ronald Farkas, MD, PhD** Clinical Team Leader DNP, ODE-I, OND, CDER, FDA

LUNCH

FDA PRESENTATIONS (CONT.)

Concluding Remarks	**Eric Bastings, MD** Deputy Director DNP, ODE-I, OND, CDER, FDA

Clarifying Questions

Open Public Hearing

BREAK

Open Public Hearing (cont.)

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

The Applicant is proposing approval based primarily on a *post hoc* comparison of 12 patients with Duchenne Muscular Dystrophy (DMD) amenable to exon 51 skipping from the open-label portion of a single study (Study 201/202) to 13 patients from an external untreated control group. The Advisory Committee will be asked to discuss and vote on whether the application has met the statutory requirements for substantial evidence of effectiveness, based on that comparison. The Advisory Committee will also be asked to discuss the evidence provided by the Applicant on dystrophin expression with eteplirsen treatment, and vote on whether the Applicant has provided substantial evidence from adequate and well-controlled studies that eteplirsen induces production of an amount of dystrophin that is reasonably likely to predict clinical benefit.

Statutory standards for approval

Although drug approval ultimately reflects a benefit-risk assessment, the statutory standards for approval are applied stepwise, with the law first requiring substantial evidence that the drug is effective. If the standard for substantial evidence of effectiveness is met, a determination must be made that the drug is safe for its intended use, i.e., that its benefits outweigh the risks, given the nature of the disease and available treatment options.

Standard Approval

Sponsors of marketing applications are required to establish a drug's effectiveness by providing "substantial evidence" of effectiveness from "adequate and well-controlled investigations."

Positive findings on clinically meaningful endpoints in two adequate and well-controlled trials are typically required, but a single highly persuasive positive trial or a positive trial combined with independent findings that substantiate efficacy (confirmatory evidence) can also support approval in some cases. The intent of the statutory requirements is to reduce the chance of an incorrect conclusion that a drug is effective when, in fact, it is not effective. In making its determination on whether the statutory standards for approval have been met, the Agency considers all the available data.

Accelerated Approval

Under the Accelerated Approval provisions, an effect on a *surrogate marker* that is determined by FDA to be reasonably likely to predict clinical benefit can support approval, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. An effect on an *intermediate clinical endpoint* - a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) and that is reasonably likely to predict an effect on IMM or other clinical benefit - can also serve as a basis for accelerated approval.

Importantly, accelerated approval does not change the statutory requirement for substantial evidence; rather, it allows FDA to utilize a demonstrated effect on an endpoint other than clinical benefit as the basis for showing effectiveness if the sponsor provides substantial evidence from adequate and well controlled trials that the drug has an effect on a surrogate or intermediate clinical endpoint. The Agency's decision on whether to grant accelerated approval is based both on the appropriateness of the endpoints selected (surrogate marker or intermediate clinical endpoint), and on whether there is substantial evidence of an effect on these endpoints. Accelerated approval cannot be used to compensate for weak or inconsistent clinical findings (i.e., approval based on marginal data, to be buttressed with better data post-approval). When accelerated approval is used, post-approval studies to verify the expected clinical benefit are generally required.

Discussion and Voting Questions

<u>Biomarker Evidence</u>

For DMD, there is obvious interest in dystrophin expression as a potential surrogate marker to support accelerated approval. Whether an effect on a biomarker such as dystrophin is reasonably likely to predict clinical benefit in DMD depends on a number of factors including, but not limited to, the reliability of the data, the magnitude of the effect on the biomarker, and confidence that the dystrophin produced is functional.

Eteplirsen's putative mechanism of action is to increase production of a truncated form of dystrophin. By Western blot, the most accurate quantitative method used by the Applicant, mean dystrophin levels after 180 weeks of eteplirsen treatment are 0.93% ± 0.84% of normal (mean ± standard deviation). The Applicant reported a control (untreated) value of 0.08% dystrophin based on retained samples from the pre-treatment biopsy in 3 patients from Study 201/201, combined with data from six patients with DMD who were not enrolled in any study. FDA

identified, however, some important limitations with respect to interpretation of the results of the untreated controls (e.g., limits of assay detection, different muscles sampled).

1. **DISCUSSION**: Discuss the evidence presented about dystrophin production, including the following:

   Committee Discussion: *The committee members did not reach a consensus on either the strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients relative to baseline, or the clinical meaning of the amount of dystrophin observed in the muscles of eteplirsen-treated patients.*

   a. The strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients, relative to their baseline.

      Committee Discussion: *About half of the committee members thought that there was evidence that eteplirsen increased the amount of dystrophin produced in the muscles of the treated patients. Among those who were not convinced, two members cited issues with the controls (lack of pre- and post-treatment biopsies in the same patients; differences in muscle groups biopsied), two had concerns about inconsistencies between dystrophin levels and clinical response, and one cited concerns about the lack of a dose-response. One committee member found it surprising that there wasn't more scientific consensus. Please see the transcript for details of the committee discussion.*

   b. Clinical meaning of the amount of dystrophin observed in the muscles of eteplirsen-treated patients, taking into consideration the range of amounts of dystrophin known to be typically present in patients with DMD and in patients with Becker muscular dystrophy.

      Committee Discussion: *Only four committee members had explicit comments with respect to the clinical meaningfulness of the amount of dystrophin observed in treated patients, and their opinions were split. One opined that the amount of dystrophin needed to impart clinical benefit is unknown, but could be very low, or very low in a subset of patients. One of the patient representatives noted that dystrophin was produced, and that the amount was sufficient to produce clinical benefit. One committee member, having opined that some dystrophin was produced, stated that we have no idea how much dystrophin would be clinically significant, or whether the dystrophin is functionally active. Another committee member, one who had not opined on whether dystrophin was produced, noted that whatever the amount of dystrophin produced, it was not clinically meaningful, based on a lack of correlation between dystrophin results and clinical results. Please see the transcript for details of the committee discussion.*

2. **VOTE**: Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?

   Vote Result: YES: 5 NO: 8 ABSTAIN: 0

***Committee Discussion**: Eight committee members voted "No", i.e. that the Applicant did not provide substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit. One committee member stated that he had pressed the wrong voting button and stated that his vote should be changed to "Yes" for the record. In explaining their "No" votes, five committee members opined that the studies were not adequate and well controlled and questioned the techniques used to measure dystrophin as well as the appropriateness of the controls. Four committee members expressed concern about the lack of correlation between the dystrophin levels and clinical measures. They agreed that even if some dystrophin was produced, there was no evidence that dystrophin production was at a level that would be reasonably likely to predict clinical benefit. The members who voted "Yes" believed that there was some difference in dystrophin production and some evidence of improvement in endpoints. One of the members who voted "Yes" stated that he was very troubled by not understanding what constitutes a clinically significant amount, but was impressed by the patients' observations. Please see the transcript for details of the committee discussion.*

Clinical evidence

Study 201/202 began as a 24-week randomized controlled study comparing three groups of 4 patients each, treated weekly with eteplirsen 50 mg/kg, eteplirsen 30 mg/kg, or placebo (Study 201). Study 201, when analyzed according to the pre-specified intent-to-treat (ITT) methods, did not show an advantage of eteplirsen over placebo on the 6-minute walk test (6MWT) after 24 weeks of treatment.

After the randomized placebo-control phase, all patients entered an open-label extension phase beginning at Week 28, i.e., Study 202. The primary clinical endpoint of Study 202 was a comparison of Week 48 6MWT results for patients originally randomized to eteplirsen vs placebo. When analyzed according to the pre-specified ITT methods, Study 202 did not demonstrate an advantage of eteplirsen over placebo on the 6-minute walk test.

The Applicant then continued open-label treatment with eteplirsen in Study 202, which is still ongoing, and is seeking approval primarily based on a *post hoc* comparison of 12 patients from Study 201 to 13 patients from an untreated external control group amenable to exon 51 skipping (from two DMD patient registries, the "Italian Telethon DMD Registry" database and the "Leuven Neuromuscular Reference Center" database).

Because of difficulty of controlling bias in historical control studies, important issues to consider include: 1) whether there are identified or possible differences between the treatment and control groups, at baseline or during treatment, that may have had an impact on clinical course; 2) whether the endpoint(s) used to assess benefit was (were) objective and assessed in a sufficiently similar way in the treatment and control groups to allow a valid comparison; and 3) whether the reported effect size is large enough to conclude that the course of patients in Study 201/202 is clearly different from the usual course of patients with DMD.

3. **DISCUSSION**: Discuss the strengths and weaknesses of the clinical evidence of efficacy provided by Study 201/202, with particular consideration of the design of the study, sample size, statistical methods, general concerns regarding a comparison to a historical control group, specific concerns with respect to the comparability of these two groups (in particular, how motivational factors and differences in assessment of physical performance outcomes may have affected the 6-minute walk endpoint and other endpoints), and any other issues that you think may be important.

   Committee Discussion: *Overall, the majority of the committee agreed that there were weaknesses to Study 201/202. One committee member noted that although placebo controlled trials can have flaws, studies with historical controls can have even more flaws and was uncomfortable with the study design of Study 201/202. Another committee member added that, considering the testimonies provided by the public, Study 201/202 might have been successful if the patient-reported results had been included. Other committee members noted that they would have liked to see a measurement of upper limb strength, which was reported to be improved in the testimonies from the public but was not captured in the North Star Ambulatory Assessment, 10-meter run/walk and 6-minute walk tests. Please see the transcript for details of the committee discussion.*

4. **VOTE**: Were decisions to administer the 6-minute walk test (vs. conclusions that the patient could no longer walk) sufficiently objective and free of bias and subjective decision-making by patients, their caregivers, and/or health care professionals to allow for a valid comparison between patients in Study 201/202 and an external control group?

   Vote Result: YES: 5 NO: 7 ABSTAIN: 1

   Committee Discussion*: A slight majority of the committee voted "No", i.e. that decisions to administer the 6-minute walk test (vs. conclusions that the patient could no longer walk) were not sufficiently objective and free of bias and subjective decision-making by patients, their caregivers, and/or health care professionals to allow for a valid comparison between patients in Study 201/202 and an external control group. These members explained that there were difficulties in assessing historical controls, that there were problems with the primary endpoints, which measured only lower body strength, and they questioned the objectivity of the conclusion that the people in the external control group were actually unable to perform the 6-minute walk test. The members who voted "Yes" agreed that the 6-minute walk test was sufficiently objective to be meaningful, and that there was no evidence of real bias. One committee member chose to abstain, explaining that the 6-minute walk, although subjective, could be a valid endpoint, but had trouble with the context in which it was used and therefore had difficulty interpreting the question to make a firm decision. Please see the transcript for details of the committee discussion.*

5. **VOTE**: What is the impact of the North Star Ambulatory Assessment results on the persuasiveness of the findings in Study 201/202?

   a. Strengthen
   b. Weaken

c. No effect

Vote Result: Strengthen: 2 Weaken: 5 No Effect: 6

***Committee Discussion**: Six members of the committee voted that the results of the North Star Ambulatory Assessment (NSAA) had no effect on the persuasiveness of the findings in Study 201/202. One panel member stated for the record that he wanted to change his vote from "Strengthen" to "No Effect." These members agreed that, overall, there was no evidence of difference between the two groups on either measure. The members who voted that the impact of the NSAA results weakened the persuasiveness of the findings in Study 201/202 noted that NSAA is a more comprehensive measure of functional assessment and explained that the persuasiveness was weakened because there were no statistically significant differences between the treated vs. the control groups. Please see the transcript for details of the committee discussion.*

6. **VOTE**: What is the impact of the other tests of physical performance (e.g., rise time, 10-meter run/walk) on the persuasiveness of findings in Study 201/202?

   a. Strengthen
   b. Weaken
   c. No effect

   Vote Result: Strengthen: 1 Weaken: 2 No Effect: 10

   ***Committee Discussion**: The majority of the committee voted that the impact of the other tests of physical performance (e.g., rise time, 10-meter run/walk) had no effect on the persuasiveness of findings in Study 201/202. These members noted that the FDA and Applicant are in disagreement in assessing rise time. They agreed that overall, physical performance measures in the other tests were secondary outcomes and that there was no evidence of difference between the two groups, probably because of the small sample size of the studies. Please see the transcript for details of the committee discussion.*

7. **VOTE**: Do the clinical results of the single historically-controlled study (Study 201/202) provide substantial evidence (i.e., evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy) that eteplirsen is effective for the treatment of DMD?

   Vote Result: YES: 3 NO: 7 ABSTAIN: 3

   ***Committee Discussion**: The majority of the committee voted "No", i.e. that the clinical results of the single historically-controlled study (Study 201/202) did not provide substantial evidence that eteplirsen is effective for the treatment of DMD. These members agreed that Study 201/202 was not a well-controlled study and based on statistical and scientific findings, substantial evidence regarding the efficacy of eteplirsen was not evident. Most committee members who voted "No" cited problems with the controls. One noted that a*

historically-controlled study could provide evidence of effectiveness, but that this trial did not. Two committee members noted that the original placebo-controlled portion of the study was negative. One member, noting the disconnect between the trial data and the patient testimonies, suggested that the patient community should be more willing to participate in controlled trials. One member who cited problems with the controls also noted that a single trial is insufficient. The members who voted that "Yes" said that substantial evidence did exist, adding that the study correlated with the testimonies presented by the public. With respect to the members who abstained, one member stated that he was torn between the data presented by the FDA and the testimonies presented by the public. One felt uncomfortable with what he thought was a leading question. Another stated that the study was not adequate and well controlled, but that he was moved by the patient testimony. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 7:36 p.m.