**FOOD AND DRUG ADMINISTRATION (FDA)**
Center for Drug Evaluation and Research (CDER)

***Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting***
College Park Marriott Hotel and Conference Center, Chesapeake Ballroom
3501 University Blvd. East, Hyattsville, Maryland
April 25, 2016

# QUESTIONS

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**

Biomarker Evidence

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:

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

    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.

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?

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.

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?

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

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

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?