Results Wire: US FDA Advisory Committee Votes Narrowly Against Accelerated Approval and Against Full Approval of Sarepta's Eteplirsen for Duchenne Muscular Dystrophy – APR 25, 2016 (PCNS)

Background

On April 25, 2016, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) voted that Sarepta Therapeutics, Inc. (Sarepta) has not 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, by a vote of 3-Yes to 7-No, with 3 abstentions.
The Committee also narrowly voted that the clinical results of the single historically-controlled study (Study 201/202) do not provide substantial evidence that eteplirsen is effective for the treatment of Duchenne muscular dystrophy (DMD), by a vote of 6-Yes to 7-No, with no abstentions.
Sarepta had submitted an application for eteplirsen for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, under new drug application (NDA) 206488.
The PDUFA goal date for the FDA decide on whether to approve the application is May 26, 2016.

Key Outcomes of Advisory Meeting

The Committee discussed the clinical meaningfulness of the data for dystrophin expression, a potential surrogate endpoint to support accelerated approval in patients with Duchenne muscular dystrophy (DMD). FDA specifically asked the Committee to consider the data for dystrophin expression as it relates to the levels that are seen in patients with Becker muscular dystrophy (BMD), a milder form of muscular dystrophy. In FDA's opinion, immunofluorescence analysis of dystrophin expression is not a reliable method to quantify dystrophin. When dystrophin was analyzed using a more reliable method (the Western blot method) in the Agency's view, the estimate of 0.9% of normal levels after 3.5 years of treatment was disappointing to the FDA, in part because it is below the level that is generally observed in patients with BMD, which is generally 3% of normal. FDA says it is not yet known which level should confer a clinical benefit, but experts have proposed that induction of approximately 10% of normal dystrophin levels may set a minimum level.

A narrow majority of the Committee, 7 of 13 members, voted that Sarepta has not 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. This would be required to support accelerated approval.

Overall, the Committee acknowledged that there is evidence of dystrophin production with eteplirsen treatment; However, a narrow majority of the Committee was unconvinced that the data meet the requirement of substantial evidence required to support accelerated approval. The Committee members who disagreed with the majority noted that comments that were made in support of eteplirsen during the open public hearing session of the meeting influenced their votes.
FDA presented data for clinical measures of improvement from the pivotal study 201/202. For the prospectively planned analysis in Study 201, there was no statistically significant difference in the

change from baseline to Week 24 in the 6-Minute Walk distance (6MWD) between eteplirsen 50 mg/kg, eteplirsen 30 mg/kg, and placebo. But Sarepta believes that eteplirsen's benefit was demonstrated in *post hoc* analyses of the 6MWD for eteplirsen-treated patients compared to external control at year 4. Sarepta reported a significant difference of 162 meters in the 6MWD, as well as a reduction in the number of boys with an estimated loss of ambulation (17% for eteplirsen compared to 85% for the external control (p=0.011). However, FDA's statistical reviewer did not agree that the data provide statistical evidence to support efficacy. FDA said the following issues negatively impact the interpretability of the study beyond the placebo-controlled period:
-Differences in steroid use between the two groups (eteplirsen-treated patients and external historical control patients),
-Possible impact of expectation bias, motivation, and coaching on 6MWD outcomes,
-Timing of the selection of patients for the external control group (3 years after study data were available),
-Unknown potential prognostic factors to match patients,
-Potential differences in how study personnel judged endpoints (6MWD and loss of ambulation (LOA)), and
-Comparison of patients by years of treatment/observation, versus age, since age correlates more strongly with function in DMD.

A majority of the Committee, 7 of 13 members, voted that the administration of the 6-minute walk test, versus conclusions that the patient could no longer walk, was sufficiently objective and free of bias and subjective decision-making by patients, their caregivers, and/or healthcare professionals to allow for a valid comparison between patients in Study 201/202 and an external control group. One of the Committee members abstained from voting on this question.

A majority of the Committee, 7 of 13 members, voted that the impact of the North Star Ambulatory Assessment (NSAA) results had no effect on the persuasiveness of the findings in Study 201/202. Among other functions, the NSAA measures the activities of standing, walking, standing f om a chair, standing on one leg, climbing onto and descending from a box step, rising from lying to sitting, rising from the floor, jumping, hopping, and running.

A majority of the Committee, 10 of 13 members, 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.

A majority of the Committee, 7 of 13 members, voted that the clinical results of the single historically-controlled study (Study 201/202) do not 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. Three of the Committee members abstained from voting on this question. This question would be crucial to support full approval.

The members who voted against full approval concluded that the pivotal study was not well-controlled, and therefore, lacks the evidence that is necessary to support an approval on the basis of a single study.

The members who voted in support of full approval said that, although they could not fully reconcile the difference between the benefit that was shown in the data presented and the benefit

that was testified to in the open public hearing, they believe there is substantial evidence of improvement, and they encouraged the collection of more data in order to address the discrepancy.

There were 52 speakers in the open public hearing. All but two of these speakers supported approval. Speakers included one politician, as well as advocacy groups, clinical trial participants and their family members, other DMD patients and their family members, physicians and scientists. For subscribers to our premium service, the comments that were made during voting will be available soon in the Final Results Wire report. This may provide additional insight into some of the members' votes, as it was clear that some Committee members were impacted by the open public hearing speaker's presentations.

At the close of the meeting, an FDA representative said that meaningful testimony from the Open Public hearing portion of the meeting had been heard, and it also noted its influence on the Committee members. The Agency stated that the public should feel assured that it will take everthing that transpired at the meeting into consideration in making its decision on whether to approve eteplirsen.

Overall Voting Results

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?
6-Yes
7-No
0-Abstain
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?
7-Yes
5-No
1-Abstain
5. VOTE: What is the impact of the North Star Ambulatory Assessment results on the persuasiveness of the findings in Study 201/202?
1-a. Strengthen
5-b. Weaken
7-c. No effect
0-Abstain
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?
1-a. Strengthen
2-b. Weaken
10-c. No effect
0-Abstain
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?

3-Yes
7-No
3-Abstain

METADATA: **Sponsor**: Sarepta Therapeutics **Drug Name**: eteplirsen **Drug Class**: exon-skipping therapy **Indication**: Duchenne muscular dystrophy