Background Analysis: US FDA Advisory Committee to Review Sarepta's Eteplirsen for Duchenne Muscular Dystrophy – APR 25, 2016 (PCNS)

Announcement

The US FDA has scheduled a Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) meeting for Monday April 25, 2016 to discuss new drug application (NDA) 206488 for eteplirsen (injection for intravenous infusion), by Sarepta Therapeutics, Inc. (Sarepta), 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.
Originally, this meeting was scheduled for January 22, 2016, but it was postponed due to inclement weather.

Indication Background

Duchenne Muscular Dystrophy (DMD) is a rare, degenerative neuromuscular disorder that is caused by an X-linked mutation in the DMD gene, a gene that provides instructions to create a protein called dystrophin. Dystrophin is important because it plays a role in the stabilization and protection of skeletal and cardiac muscle.

In male patients, an alteration of the one X chromosome leads to the condition. In females, both X chromosomes need to carry the mutation to cause the disorder. Therefore, it usually affects males, with a worldwide incidence estimated at 3,500 to 6,000.

Those with DMD experience severe progressive muscle loss which leads to an inability to walk and to premature death. Death is typically due to cardiac or pulmonary issues. Males with DMD typically live into their twenties. In the U.S., there are no approved treatments. Current standard of care is to treat patients' symptoms. Corticosteroids have been used to slow muscle decline.

Patient advocacy groups for DMD have been exceptionally active and vocal in the push for new treatments. For the first time, the issuing of FDA Draft Guidance for Industry was preceded by submission of a proposed Draft Guidance for the development of DMD treatments from an advocacy group. Due to the strong patient advocacy and public interest, the FDA anticipates a large number of speakers in the Open Public Hearing (OPH) portion of the meeting, and therefore it has extended the scheduled time for the OPH from 1 hour to 2 hours.

Antisense Therapies

-Eteplirsen
Eteplirsen (e-TEP-ler-sun), a.k.a AVI-4658, is an antisense therapy. Antisense therapies work through regulation of gene expression. When a gene segment that contains coding for a protein, also called an exon, is known to be associated with a disease, one can synthesize a nucleic acid that binds to the site of mutated exon, modifying its activity.

Thirteen percent of patients who have DMD have a genetic mutation on an exon that has been labeled “exon 51”. Eteplirsen is designed to bind to the exon, causing its activity to be skipped. This “exon skipping” allows for the production of shortened, but still useful forms of dystrophin.

Eteplirsen consists of a short segment of RNA bound to a phosphorodiamidate morpholino oligomer. It is charge-neutral, which some people say avoids potential protein binding and off-target effects that may occur with charged treatments. It is formulated for once-weekly intravenous (IV) infusion.

-Drisapersen
On January 14, 2016, the FDA issued a Complete Response Letter in response to an application for another product that skips exon 51, BioMarin Pharmaceutical’s Kyndrisa (drisapersen), subsequent to the product’s review at a PCNS meeting on November 24, 2015. The FDA concluded that the standard of substantial evidence of effectiveness was not met.

In the FDA Briefing Document that was posted in advance of the PCNS meeting for Drisapersen, an FDA Clinical Reviewer noted that two small phase 2 studies showed a significant or near significant treatment difference in the distance patients can walk in 6 minutes (6MWD or 6MWT), but the large phase 3 trial was negative. The review also raised a concern about safety and about the potential for unblinding based on the injection site adverse events that were seen. In addition, the FDA disagreed with post hoc subgroup analyses that were submitted by BioMarin because they were found to be highly sensitive to small differences in cutoffs for age and 6MWD and to other statistical manipulations, and therefore FDA concluded they lacked credibility. The Agency also commented on the evidence for increased dystrophin saying, “It is greatly concerning that a number of biomarker studies suggest that, contrary to initial published reports, drisapersen has little effect on increasing dystrophin levels, the putative mechanism of action.” The Agency concluded in its briefing document, “while there may be some evidence suggestive of efficacy of drisapersen, the evidence is inconsistent and in some cases contradictory, and does not reach the level of substantial evidence.” Furthermore it said “the evidentiary standards for effectiveness are not lower for biomarker endpoints used to support Accelerated Approval, nor should Accelerated Approval be used to compensate for weak or inconsistent clinical findings. Negative clinical findings in studies of adequate design and conduct to assess such findings would ordinarily preclude Accelerated Approval on the basis of associated biomarker effects.”

The FDA did not ask the Committee to vote on whether to recommend approval of drisapersen but to vote on whether key aspects of the data strengthen, weaken, or have no effect on the interpretation of the clinical results. A majority of the Committee thought that key aspects of the data that were highlighted by the FDA either weakened or had no effect on (and did not strengthen) the interpretation of the clinical results. The Agency also asked the Committee to discuss the overall strengths and weaknesses of the data for the proposed indication, in a ninth question that was added on the day of the meeting. Input from the Committee included the following:

- The FDA should give more weight to the phase 3 study results than to the results of the smaller phase 2 studies.
- Drisapersen might be appropriate to be used in a narrow group of patients who are not in rapid decline, but the Committee also thought the population would need to be better defined and studied further.

- There was evidence for only a small change in dystrophin expression, one that failed to correlate to clinical outcomes.
-In response to comments that were made in the OPH, the Committee felt that, in the context of a fatal disease, the parents of patients and their physicians are best suited to weigh safety concerns, but only if the drug is proven to be efficacious. In this case, it was challenging because the efficacy data were not conclusive.
- Although there were no deaths in the study, it was noted that some of the adverse events that were seen in the clinical development program present a risk of mortality.

-Ataluren
On February 22, 2016, the FDA issued a Refuse to File (RTF) letter to PTC Therapeutics in response to their NDA submission for the proposed DMD treatment Translarna (ataluren), which was started as a rolling NDA submission in December 2014. In the letter, the FDA stated that both the Phase 2b and Ataluren Confirmatory Trial (ACT) DMD trials were negative and do not provide substantial evidence of effectiveness. The FDA also said that the company's adjustments to the (ACT study were post hoc and therefore not supportive of effectiveness. The FDA also said the NDA failed to include adequate information about ataluren's abuse potential, which is required for new molecules that cross the blood-brain barrier. The FDA had previously issued an RTF leter in 2011 on the grounds that the submission did not contain substantial evidence of effectiveness based on the single placebo controlled Phase 2b clinical trial that at the time was the basis of the NDA submission.

In contrast with the U.S., on July 31, 2014 PTC Therapeutics received conditional marketing authorization for Translarna (ataluren) in the E.U. to treat patients aged 5 years and older with DMD who are able to walk. Conditional approval means the company is required to provide more evidence over time, and it is allowed only for drugs that are intended for use in an area in which there is unmet medical need. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency reassesses the conditional approval on an annual basis, and Translarna was scheduled to submit the results of a confirmatory study in the fourth quarter of 2015. Based on a review of this report the CHMP will recommend either withdrawal or conversion to standard approval.

Clinical Trials of Proposed Indication

Summary of FDA Briefing Materials from the Postponed January 2016 Meeting

Below is a summary of the FDA briefing document for the postponed meeting on January 22, 2016. It is important to note that FDA's earlier briefing document does not include a review of a submission that was made by Sarepta on January 8, 2016 which included four-year clinical effectiveness data. Some of these data were presented by Sarepta in an addendum to their earlier briefing document, and these data are summarized in this report in the subsequent section, **Summary of Company Briefing Materials from the Postponed January 2016 Meeting.** In addition, the FDA briefing document did not include responses to a series of clarifications Sarepta made in response to the FDA briefing document in the same addendum, which are also described below**.**

In the earlier briefing document, the FDA stated, "Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options, we cannot approve drugs for which

substantial evidence of effectiveness has not been established." The Agency seemed unconvinced about the efficacy of eteplirsen.

In regard to safety, the clinical team leader's memorandum stated "the serious and severe adverse events that occurred were generally consistent with events expected in DMD." In addition, the briefing memorandum to the Committee stated, "No safety signal of significant concern has been identified for eteplirsen, although the clinical safety database for eteplirsen is small, as only 12 patients were exposed for one year or longer, with only 36 patients exposed for 24 weeks or longer (the applicant included safety data from ongoing open-label studies). As a consequence, the one-year database only has adequate power to assess the frequencies of the more common adverse events. Less frequent events, possibly serious, may have been missed because of the small database."

In regard to efficacy, the FDA explained that the pharmacodynamic and clinical effects of eteplirsen are potentially demonstrable via three methods: 1) expression of an altered messenger RNA (mRNA) in muscle (pharmacodynamic); 2) increased production of dystrophin protein in muscle (pharmacodynamic); and 3) improvement or preservation of muscle function (clinical).

For the first method, altered mRNA expression, Sarepta used a standard technique called reverse transcriptase polymerase chain reaction (RT-PCR), and reported that this testing confirmed exon 51 skipping in all patients. FDA noted that there were methodological concerns with the RT-PCR testing in the first three biopsies in Studies 201/202 (the pivotal study and its open-label extension study), whichwere addressed by the fourth biopsy. The Agency said RT-PCR is limited, in particular, "PCR is a highly sensitive technique that can detect even a few copies of messenger RNA. Because even a trivial PCR signal is interpreted as "positive," this biomarker provides little support of efficacy. The RT-PCR finding may, however, provide evidence that eteplirsen leads to at least some degree of exon 51 skipping."

For the second method, increased dystrophin, FDA explained there are two different methods: immunofluorescence (IF) and Western blot (WB). FDA prefaced the IF results with a description of a limitation with the technique, saying "It should be understood that immunofluorescence can overestimate the amount of dystrophin in tissue sections. This is because a muscle fiber can be considered "positive" if it exhibits any staining at all, even if the level of dystrophin is very low." The Agency noted inconsistency with the IF results, saying, "the applicant's findings on percent positive fibers are based on a comparison between a group of 4 patients who received eteplirsen 30 mg/kg and a group of 4 control patients at Week 24. There was a second comparison between a group of 4 patients who received eteplirsen 50 mg/kg and the group of 4 controls at Week 12. With these two comparisons of eteplirsen to placebo, there was a positive finding for only one of the doses (the lower dose) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group, and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point."

The Agency referred to WB as "the most accurate quantitative method used by the applicant." Using this method, mean dystrophin levels after 180 weeks of eteplirsen treatment were reported to be about 0.9% of normal (range <0.25% to 2.5%), with a relative increase of dystrophin of about 3-fold compared to the trace levels typically present in patients with DMD (about 0.3% of normal).

FDA also noted that there was not a strong correlation between the WB and IF data.
For the third method, clinical effects reflecting muscle function, FDA prefaced the discussion by explaining that Study 201 failed its primary endpoint, dystrophin positive fibers, and therefore the secondary endpoint, in this case, a test of the distance patients can walk in 6 minutes (6MWT), cannot be formally tested. Nonetheless, the FDA reported that, based on informal testing, "there was no nominally significant difference on the 6MWT between eteplirsen 50 mg/kg, eteplirsen 30 mg/kg, and placebo in the prospectively planned intent-to-treat (ITT) analysis in Study 201."
FDA said that Sarepta highlights a post-hoc analysis on a modified population in which two patients in the lower dose group who became unable to ambulate soon after the study start were removed from the analysis.

FDA discussed Sarepta's additional analysis of 6MWT data from Study 201/202 in comparison to historical data from two DMD patient registries. The company has reported a statistically significant result in favor of the low dose, with a difference of 151 meters over historical control. However, FDA identified three issues with their analyses, as follows:

First, the intent-to-treat (ITT) analysis, including all randomized patients, was negative for the comparison between the eteplirsen and placebo groups. In that setting, all subsequent analyses should ordinarily be considered exploratory and hypothesis-generating.
Second, patients in Study 202 appeared to be receiving optimal care, including intensive physical therapy and intensive steroid regimens. FDA asked the applicant to establish that treatment modalities in the historically-controlled population were similar, so that the historical group would be an appropriate control for the Study 202 patients.
Third, FDA noted that for most of its duration, Study 202 was open-label with all patients receiving eteplirsen, and that performance on the 6-minute walk test could be influenced by motivation and coaching. FDA expressed concern that open-label trials are susceptible to bias on the part of investigators, patients, and parents.

Furthermore, the FDA noted, "the clinical course of the 12 patients participating in Study 201/202 appears to be within the expected natural history of DMD" on the basis of scores on the North Star Ambulatory Assessment (NSAA) and the loss of ability to rise from the floor. FDA describes the NSAA as being "specifically designed to measure functional ability in ambulatory patients with Duchenne muscular dystrophy," and FDA said, "The NSAA is a comprehensive outcome measure, and arguably more fully reflects function in DMD than the 6MWT."

FDA explained that two pathways for accelerated approval (AA) were discussed with Sarepta: 1) AA using 6MWT as an intermediate clinical endpoint; and 2) AA using dystrophin data as a surrogate endpoint.

In regard to the first option, FDA said, "Study 201 clearly failed to show an advantage of eteplirsen over placebo on 6-minute walk distance in the placebo-controlled trial. The specific finding proposed by the applicant as supporting accelerated approval is the comparison of 6-minute walk distance between the 12 patients in Study 201/202 and historical controls, where the control patients were selected post hoc. There are significant concerns regarding the ability to draw valid conclusions from this historically-controlled comparison. Moreover, comparisons between patients in Study 201/202 and patients in a related development program who had received placebo suggest

that the change in 6-minute walk distance with eteplirsen was consistent with the natural history of the disease."

In regard to the second option, FDA wrote "The apparent treatment effect could be expressed as a 3-fold increase over the trace amount present at baseline, but relative changes can be difficult to interpret. The mean dystrophin level in patients who had been treated with eteplirsen for some 180 weeks was on average 0.9% of normal, far below levels observed in a milder form of muscular dystrophy known as Becker-type muscular dystrophy (BMD). The minimum level of dystrophin that might be reasonably likely to predict clinical benefit in patients with BMD remains unknown, but experts in DMD have stated that levels less than 3% of that of normal healthy muscle are generally associated with the typical DMD phenotype, and have proposed that "induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit." In addition, so called "exon 51-model" BMD patients, who have the same truncated form of dystrophin that would be produced by eteplirsen in DMD patients, and experience a mild disease, express truncated dystrophin at levels reported to range from 50% to 100% of normal.

Draft Points to Consider from the Postponed January 2016 Meeting

FDA did not posted the draft questions for the meeting; but they posted "Draft Points to Consider" (shown below), which are precursors to the draft questions. In these, FDA asked the Committee for input on the clinical meaningfulness of the data for dystrophin expression, for an overall interpretation of Study 201/202, and for recommendations for the possible design of any future efficacy and safety studies that might be necessary.

1. Consider the data for dystrophin expression, including the following

a. Experimental methods, including consideration of accuracy, reliability, reproducibility, etc.

b. Potential clinical meaning, including consideration of amount of dystrophin relative to patients with Becker muscular dystrophy, functionality of the truncated dystrophin, and percent of muscle fibers with detectable dystrophin.

2. Consider the data for clinical measures, including the following

a. Design and potential interpretability of Study 201/202, including consideration of a) the placebo-controlled period, and b) comparison of the open-label experience to natural history.

b. Results of Study 201/202 in the context of the study design.

3. Consider the possible design of any future efficacy and safety studies that might be necessary.

Summary of Company Briefing Materials from the Postponed January 2016 Meeting

In regard to the efficacy of eteplirsen, Sarepta wrote, "The benefits of eteplirsen are demonstrated by a significant difference in the 6MWT of 151 meters compared to external control and a reduction in the number of boys with a loss of ambulation (17% for eteplirsen compared to 46% for the external control cohort of exon 51 skippable patients)." Sarepta said that their assessment of NSAA in treated patients compared to external control shows a slower rate of decline and, in addition, treated patients experienced relative pulmonary function stability, with an annual decline of 3.2% on percent force vital capacity predicted (FVC% predicted), compared to an external cohort of patient level data showing an annual decline of 5.8% on FVC% predicted.

In an addendum to their main briefing document, Sarepta presented data requested by the FDA for loss of ambulation (LOA) at 4 years. The company wrote, "All 10 of the eteplirsen boys who were ambulant at time of NDA submission remain able to walk at Week 216. Their ages at this point in the study range from 11.8 years to 15.2 years, with 4 of the boys aged 14 or older. This is in contrast to what was stated in the FDA Briefing Document for drisapersen, 'by age 10-14, DMD patients become wheel chair bound.'

In regard to safety, Sarepta said that eteplirsen is well tolerated with no apparent signal of safety risks. The company says, although the safety database may not be capable of detecting rare events, "this needs to be weighed against the certainty of relentless disease progression and premature death for boys with DMD without treatment."

Sarepta emphasized that the FDA has the authority and specific direction from Congress to exercise flexibility in considering the data.

The company also reported that it is committed to completing the confirmatory trial that is underway.

Clarifications in Sarepta's Addendum to Briefing Materials from the Postponed January 2016 Meeting

In the aforementioned addendum, Sarepta also made several clarifications to statements from the FDA. First, on page 7, FDA wrote, "With these two comparisons of eteplirsen to placebo, there was a positive finding for only the lower dose (30 mg/kg) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point."

Second, on page 13, FDA wrote, "Arguably, placebo-treated patients who were blinded to treatment assignment from other controlled trials are more appropriate as matched controls than registry patients, as they may receive special care and attention as trial participants, and may be more highly motivated." In response, Sarepta wrote, "The study was designed to see whether dose (50 mg/kg vs. 30 mg/kg) or duration was the most important criterion to enable consistent dystrophin production. Duration of therapy was observed to be the critical variable when interpreting dystrophin levels. 12 weeks does not represent a clinically relevant duration of therapy (FDA BD page 26 of PDF). Significant dystrophin levels were measured at Week 24 for the 30 mg/kg dose, and, importantly, at Weeks 48 and 180 for both the 30 and 50 mg/kg doses by all dystrophin assay methods."

Sarepta added that the placebo patients from another study, as referenced by the FDA are not appropriate for comparison with the eteplirsen- treated patients (in the FDA's Briefing Document on pages. 8, 9, 40-44, and 50) because the baseline characteristics are not comparable between eteplirsen and the proposed placebo group. The placebo group included boys <7 years old and many patients with baseline 6MWT >440 meters, which is outside the eteplirsen trial's inclusion criteria. Placebo patients were followed for only one year, whereas eteplirsen-treated patients were followed for 3 or more years. Due to the ambulatory requirement at study entry, older placebo patients (e.g., ≥11 years) were a group of pre-selected, better performing subjects. Sarepta argues that comparing the first year of an 11-year-old-at-baseline placebo patient to the third year of a 9-year-old boy with

3 years of eteplirsen treatment is not a valid comparison due to the difference in duration of observation, as well as the biased selection of the 11-year-old ambulatory placebo boy, irrespective of both patients having the same age at last assessment. Sarepta asserts that a comparison of eteplirsen-treated patients to the appropriately matched external control shows that more than one year is required to observe a divergence in disease progression between the two groups.

FDA stated on page 29, "It is important to note that the applicant digitally processed dystrophin images in their background material (images in Appendix 12, pg. 29) in such a way that low intensity values were preferentially increased to produce a higher intensity and higher contrast image." In response, Sarepta says the digitally processed images referenced by FDA in this statement were included in the briefing document for demonstration purposes only, and it is important to note that the referenced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.

FDA stated on page 30, "Biomarker studies on the 4th biopsy obtained at Week 180 were conducted by the applicant with technical advice from FDA. However, the reliability of results remains questionable for a number of reasons, including the lack of independent confirmation." In response, Sarepta said, "The methodology for dystrophin analyses of the fourth biopsy tissue samples, including confirmatory assessments of percent dystrophin-positive fibers (PDPF) analysis performed by 3 independent pathologists, were agreed with FDA prior to conducting any analyses of the fourth biopsy tissue samples. In accordance with the mutually agreed-upon protocols for the assessment of dystrophin-positive fibers in DMD muscle biopsy samples from the fourth biopsy obtained at Week 180, 3 independent pathologists performed a blinded assessment of the randomized muscle fiber microscopy images, which independently confirmed the results obtained by the pathologist at Nationwide Children's Hospital (NCH). Assessment of PDPF at NCH indicated a significant increase in PDPF score ($p<0.001$) relative to untreated control samples. This increase in PDPF score was confirmed by the 3 independent pathologists ($p<0.001$)."

FDA stated on page 31, "Random measurement error can be large in comparison to the estimated amount of dystrophin." In response, Sarepta said, "The random measurement error of our Western blot protocol for measurement of dystrophin levels was well below the observed difference between untreated and treated Week 180 biopsy samples. A rigorous validation of the Western blot method was reviewed by the FDA prior to Week 180 biopsy analysis. Validation data demonstrated a % CV of +/- 50% and a linear range ($R2>0.9$) of sensitivity extending as low as 0.25% of normal." (CV=Coefficient of variation)

FDA stated on page 34, "In this context, the applicant selected three BMD patients as comparators for the Week 180 dystrophin studies, one of whom had low dystrophin level of about 2% of normal. However, the BMD patients selected by the applicant do not appear representative, and this patient may correspond to one of the rare BMD patients with very low dystrophin levels." In response, Sarepta said, "BMD patient samples were not chosen to be representative; rather, they were selected in response to an FDA request to assess the relationship between dystrophin as measured by Western blot and immunofluorescence fiber intensity. Therefore, BMD samples were obtained that represented low, middle, and higher ranges of dystrophin expression. A comparable Western blot analysis-IHC correlation was presented by Hathout, et al. (MDA 2015 Scientific Conference poster, FDA-NIH workshop on measuring dystrophin, 2015), where BMD biopsies were chosen to

represent low- and mid- level dystrophin expression. Consistently, their BMD low patient biopsy was 2% of normal."

FDA stated on page 35, "There is no simple or reliable way to compare estimates of dystrophin amount derived from immunofluorescence with estimates derived from Western blot." In response, Sarepta countered that correlation between dystrophin quantification by Western blot and IHC methods has been demonstrated by multiple laboratories (Taylor, 2012; Anthony, 2011; Anthony, 2014; Hathout, 2015 FDA Workshop on Measuring Dystrophin).

In response to the FDA statement on page. 38, "As the duration of exposure in Study 202 increased, the applicant proposed comparing the clinical course of treated patients to historical controls," Sarepta said "The proposal to compare with historical control patients originated from the FDA. Specifically, a requirement to compare the clinical course of treated patients in Study 202 to matched patient-level historical control data was made by the FDA at the March 2014 guidance meeting, and reiterated at the September 2014 pre-NDA meeting. Sarepta had proposed an open-label confirmatory study comparing treated patients to concurrent (not historical) untreated patients with exon deletions not amenable to skipping exon 51 (i.e., the PROMOVI study)."

FDA stated on page 47, "Finally, as the sponsor's natural history study proceeded, some patients left to enter interventional clinical trials, further decreasing the similarity of the natural history cohort to the eteplirsen patients." In response, Sarepta said, "The 2 external control patients who entered interventional trials did not diminish the comparability of the natural history cohort. Two types of sensitivity analyses were performed to confirm the magnitude of difference remained over 100 meters and maintained nominal significance: MMRM using all available data and Last Observation Carried Forward imputation (conservative analysis assuming that the 2 control patients did not decline)." (MMRM = mixed model repeated measure)

FDA stated on page 69, "The robustness of the study result is a concern since a single patient could change the results substantially." In response, Sarepta said, "This statement is inaccurate. A comprehensive sensitivity analysis was performed in order to address any potential issue regarding robustness of the data. Specifically: Two patients were removed: the best performing eteplirsen and the worst performing external control patient. Results demonstrated a robust 6MWT treatment advantage of >100 meters with nominal significance."

Regulatory Background

U.S. Regulatory Background

May 26, 2016 –PDUFA date
January 22, 2016 – Initially scheduled date for the PCNS meeting, subsequently postponed to April 25, 2016
January 8, 2016 – Sarepta submitted 4-yr clinical effectiveness data that prompted the FDA to extend the initial PDUFA date by 3 months to allow time to review the new data.
June 26, 2015 – Sarepta completed their rolling NDA submission for eteplirsen using the accelerated approval pathway.
Designations: Orphan Drug, Fast-Track, Priority Review, Rare Pediatric Disease Designation

Relevant Guidance: Draft Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment (June 2015).

Accelerated Approval: The Draft Guidance offers two approaches for accelerated approval (AA). One approach is to submit data for a biomarker that has been validated as a surrogate endpoint that is reasonably likely to predict clinical benefit. The other is to submit data for an "intermediate clinical endpoint," which is defined as a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity and mortality (IMM) and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit.

Adverse Events: From the Draft Guidance: "Adverse events of special interest for drugs for the treatment of dystrophinopathies include exacerbation of autoimmunity to dystrophin or other muscle components. Exacerbation of cardiac disease may be a concern for drugs that increase physiological stress on the heart by increasing the amount or activity of skeletal muscle, or for drugs that could directly affect cardiac dystrophin."

Ex-U.S. Regulatory Background

Sarepta has not announced its plans for regulatory filings outside the U.S.

What's Next?

Tarius will send a Briefing Summary after briefing materials are posted to FDA's website (typically within 2 business days of the meeting). This report will provide a summary of the FDA and the Sponsor's briefing materials.
Tarius will send a Results Wire soon after the meeting. This report will include the voting outcomes, if applicable, and key outcomes of the discussion.

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