

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
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Food and Drug Administration

SUMMARY

This memorandum explains the CDER's final decision on the above application. I have read the reviews and recommendations by Drs. Unger (Office level), Bastings (Division level), Farkas (Cross-Discipline Team Lead), Breder and Rao (Clinical Reviewers), Ling (Statistical Reviewer), and Bhattaram, Wu, and Rogers (Clinical Pharmacology Reviewers). In addition to the review memoranda, I have also reviewed the Advisory Committee briefing materials, pertinent portions of the sponsor's submission, and multiple scientific statements submitted by the public, including a letter from a large number of DMD experts.

The review team has done an exemplary job in performing a detailed evaluation of the data submitted with the application. Nevertheless, I disagree with certain of their findings and come to a different conclusion, as discussed below.

I find that the data contained in NDA 206488 meet the standard for accelerated approval under 21 CFR 314.510 based on the surrogate endpoint of increased dystrophin protein production, a surrogate endpoint that I conclude is reasonably likely to predict clinical benefit.

DISCUSSION

Extensive analyses have been performed by the team on the clinical results of the long-term experience of 12 patients administered the drug, and I will not recapitulate these.

Approval under 314.510 is based, among other things, on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Below, I discuss how both of parts of this standard are met.

A. Are the Data on Dystrophin Protein Production From One or More Adequate and Well-Controlled Studies?

The characteristics of adequate and well-controlled studies are laid out in 21 CFR 314.126. Three lines of evidence are pertinent to the conclusion that eteplirsen results in increased dystrophin production.

- Production of an appropriate mRNA transcript
- Quantitative assessment of dystrophin content in muscle biopsies by Western blot
- Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry (IHC) techniques

The sponsor provided data demonstrating an increase in mRNA expression following treatment with eteplirsen. The drug's proposed mechanism of action is to bridge a section of the pre-RNA to result in a shorter mRNA with an open reading frame, e.g., "exon skipping." In this case, the production of an appropriate mRNA transcript has been documented by PCR and Sanger sequencing. Although this establishes proof of mechanism, it does not mean that there is increased protein production.

In the following, I discuss the assessments related to dystrophin protein production (2. and 3.) in some detail. Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them. With FDA's assistance, the sponsor improved the design and conduct of the assays and performed repeat biopsies on 11 of 12 patients at week 180. The control samples for these week 180 biopsies were stored baseline tissue (in 3 of 11 subjects) and baseline biopsies from subjects with exon 51 amenable mutations enrolled in another trial by the sponsor. FDA reviewers had the following concerns about these controls, leading them to conclude that the studies were not adequate and well controlled.

1. Most of the baseline biopsies were not from the same subjects as the week 180 biopsies (as the original tissue had been used up for the previous assays). Given this, the control subjects could differ in unknown ways from the test subjects.
2. The biopsies taken at week 180 were from different muscles in the upper extremity than the baseline biopsies, including subjects with baseline tissue as well as for control samples. It is hypothesized that there may be differences in dystrophin protein content among various muscles in DMD patients.
3. The existing baseline biopsies for the three subjects with 180 week data had been stored frozen for several years and may have changed (apparent decrease in dystrophin protein content) over time.

In my judgment, these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion. The non-treated control subjects were very similar in age and dystrophin mutation site to the treated subjects (sponsor Appendix 10, AC briefing package). The single deltoid muscle biopsy in the untreated control group (subject 7, sponsor Appendix 14, AC briefing package) had replicate dystrophin levels of 0.3% and below the limit of quantification, averaging out at below 0.3%, and not different than biceps biopsy results in other patients, suggesting

that variations in upper extremity biopsy site (concern b above) did not result in large differences in the findings. There was little difference in the dystrophin protein content found in the stored baseline samples and the frozen samples, as discussed below.

The data submitted with the original application, supporting the finding that eteplirsen increases the production of dystrophin protein, come from the quantitative assessment of (internally truncated) dystrophin in muscle tissue by Western blot using the controls described above. Much of the controversy around this method relates to the fact that the apparently achieved dystrophin levels are very much lower than originally hoped (and previously claimed by the sponsor and investigators).

In the 180 week assessment, the three subjects with baseline biopsies available had baseline dystrophin levels (reported as % of normal) below the level of quantification of the assay used (0.25%). These results were similar in magnitude to the baselines of the six additional control biopsies drawn from subjects in another study (highest level 0.37%). At week 180, two treated subjects had (an average of replicate) dystrophin levels above 2%, two had over 1%, and two additional had about 1%. Of these individuals, two subjects having both baseline and week 180 samples had clearly increased levels at week 180 compared to baseline. (The third subject with a baseline sample did not consent to a week 180 biopsy). Unsurprisingly, some subjects had week 180 dystrophin levels similar to the overall baseline control levels. Not all individuals are expected to respond to a drug intervention. The issue is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled. The following data are relevant to this issue.

Because the original data on the presence of dystrophin by Western blot suffered some difficulties in interpretation because of lack of availability of baseline samples from most patients, the sponsor of this application submitted, subsequent to the Advisory Committee meeting on this drug, additional Western blot data from 12 patients with baseline and 48 week eteplirsen exposure, using baseline and post-treatment muscle biopsies from the same patients and muscle groups. This experiment clearly shows, using adequate controls, that the drug increases dystrophin protein production in some of the patients. The mean baseline dystrophin values in this study were very similar to the mean baseline values in the 180 week study. The achieved levels of dystrophin in these patients are lower than those seen in the Western blots from the week 180 patients. Only 2 of 12 patients achieved a level over 1% of normal control. It is not known if this result is due to a shorter duration of drug exposure or to other factors. Putting together the 180 week data and the additional 48 week data, I conclude that there is substantial evidence from Western blot experiments of increased dystrophin protein production, albeit at a low level.

A finding of increased dystrophin was also seen in several IHC assays performed by the sponsor. Both assays were originally performed with baseline and several pre-180 week assays by the sponsor as a part of the clinical trial. The validity of the results of these assays were questioned by FDA because of methodological problems in their conduct, as documented in the primary clinical review and in the inspection report. Therefore, I will not further consider the results of these original assays. As discussed for the Western blot above, the sponsor responded by performing an additional 180 week biopsy and repeating the assays. Baseline tissue was available, as for Western blot, from recut samples

in only three cases. In one of these, the subject did not consent to a biopsy at 180 weeks. To supplement the three baseline samples the sponsor included six other untreated patients from a different trial, as discussed above for the Western blot. In both assays, greater staining or intensity was observed after drug exposure at week 180 compared to controls. The results are described in more detail below.

A Percent Dystrophin Positive Fibers analysis was a semi-automated evaluation performed at 180 weeks and compared to the controls used for the 180 week study as discussed above. The percentage of positive fibers was assessed using a blinded read by Nationwide Children's Hospital and by three independent pathologists through Flagship Biosciences. The technique used to assess percent positive fibers was modified from the original assay in the following ways:

1. A computer algorithm (MuscleMap from Flagship) that performs non-linear mapping of all fibers was used for consistent and automated analysis of low intensity values, in contrast to a manual and non-standardized fiber counting technique in the prior assay.
2. The images were inverted and amplified to score the total fibers (the denominator for the percent positive fiber scoring).
3. An isotype matched secondary antibody staining step was incorporated to confirm lack of non-specific staining and reduce background noise. The background signal was subtracted from test sample values in calculation of percent intensity.
4. 8% of the images for re-analysis were blinded, renamed, randomized, and rotated 180 degrees.
5. A rejection factor for the inter-rater analysis score of <4 was established.
6. The images were acquired in a more systematic and random fashion to minimize bias, with predefined rules for random sampling of fields and avoiding artifacts.

These changes were likely to result in a more conservative reading of Percent Dystrophin Positive Fibers, and indeed the results, including the new untreated baseline controls, were read at 1.1% positive fibers (in contrast to a higher result in the prior baseline using the original technique). The 180 week cohort had a score, using this technique, of 17.4% positive fibers, showing a statistically significant difference. Now, these results are subject to the same caveats as discussed for the Western blot (1-3 above), in that there were only two baseline to 180 week pairs, that the baseline samples had been frozen for years, and that the external controls might differ in some way. So, these results cannot stand alone.

Other reviewers have pointed out that the (much higher) baseline values for Percent Positive Fibers from the original experiment are not very different from the 180 week values in this new experiment. However, I would point out that experimental conditions changed quite a bit, and very low values for all the external controls, statistically comparable to the frozen baseline results, were obtained in this recent experiment, suggesting that it returned a more conservative result. I do not believe that comparison of the original baseline data, obtained under one set of experimental conditions, can be compared to the later 180 week results, done under different, more optimized conditions and yielding very different results for new (external control) baseline samples.

The sponsor also performed a Mean Relative Fluorescence Intensity assay for dystrophin. This assay is commonly performed by laboratories evaluating DMD patients and is intended to be a semi-quantitative evaluation of dystrophin content. Using the six external baseline samples and the three stored study patient baseline samples, the mean intensity approximately doubled from baseline to 180 weeks. The technique for this assay did not change significantly from the technique used in the assay done as part of

the original protocol, and the baseline means for the patient samples were roughly comparable to the baseline means obtained in the new experiment.

Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure). The accompanying microscopy images also demonstrate correct localization of the molecule within the muscle fibers, a very important factor in any translation to clinical benefit.

In summary, I conclude that there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.

B. Is the Effect on the Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit”?

In this case, the standard for clinical benefit does not require “cure” or “conversion to Becker MD (BMD) phenotype.” Clinical benefit encompasses improvements (including slowing of disease progression) in how an individual feels or functions, or an improvement in survival. There is no question that, for DMD patients and their families, small improvements in function or delays in loss of function are meaningful benefits. Therefore, the question is:

What amount of increase in dystrophin production is reasonably likely to predict clinical benefit (even small benefits)?

The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease. The following summarizes the existing scientific literature on this topic and the challenges in interpreting it.

1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective.

Experts usually classify patients clinically as DMD (severely affected at a young age); intermediate MD (also called DMD/BMD); or BMD, which can range from severe BMD to asymptomatic individuals with biochemical abnormalities, usually increased creatine phosphokinase (CPK). There is clearly a wide spectrum of disease wherein the ends of the spectrum are easily distinguishable, but the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized. In part, this is because “intermediate muscular dystrophy” (IMD) is less common, due to the consequences of having either in-frame mutations with a truncated protein expressed (leading to BMD) or out-of-frame mutations with little-to-zero protein expressed (leading to DMD), as discussed below.

2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from IHC studies using a variety of techniques and antibodies.

Anthony, et al., (*Neurology*, 83, 2014) in a collaborative cross-laboratory study, investigated the variability of techniques used to quantify dystrophin in individuals with muscular dystrophy. Blinded tissue sections from three DMD and three BMD muscle biopsies were tested in five

different laboratories accustomed to performing dystrophin quantification. Estimates of dystrophin expression using a somewhat standardized IHC technique were about 20%, 11% and 10% of normal for the three DMD samples, on average among the laboratories. Corresponding estimates of dystrophin content by Western blot, using an actin antibody to normalize for loading, but not a serially diluted standard control, resulted in dystrophin estimates of about 11%, 0, and 0.4% respectively, with fairly high CV's. Therefore, in this small sample, repeated across five experienced laboratories, IHC estimates were about 10 percentage points higher than Western blot estimates.

Significantly higher estimates by IHC by fluorescence intensity (overall about 23% of normal) than by Western blot were also seen in the evaluation of week 180 muscle biopsies in the Sarepta trial. Because much of the historical data on protein content vs phenotype has been reported using IHC analysis, extrapolating these findings to the current trial data is challenging. Additionally, Anthony et al., found that the inter-laboratory variability was greatest for the low levels of dystrophin found in the DMD patients. Western blot data in the literature quantifying dystrophin and relating it to phenotype is often from experiments that were not designed to distinguish among dystrophin levels below 10% of normal. These may have been reported out as "less than 10%." From this sponsor's well-controlled studies, the analytically accurate dystrophin baseline for many DMD patients might be in the range of 0.02-0.35 % normal, hence previous estimates of 5-10% might be an over-estimation using non-standardized and semi-quantitative methods.

3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions

Significantly, if the epitope recognized by the antibody is modified by the deletion, the dystrophin isoform may not be recognized and a result read out as zero. For this reason, recent studies use multiple antibodies against known regions. Additionally, muscle biopsies in patients with BMD and DMD may be quite variable in degree of fibrosis and fatty replacement; this may decrease the reproducibility and representativeness of muscle biopsy estimates of dystrophin content by Western blot. Additionally, imaging methods, choices for normalization, biopsy handling, background standing, and a multitude of other experimental conditions can influence results.

4. The phenotype is significantly influenced by *dystrophin isoform quality* as well as *dystrophin quantity*.

Dystrophin is a very large protein with multiple functional domains. Generally, DMD results from an out-of-frame mutation (often a deletion) that leads to an unstable or unreadable mRNA transcript. Thus, DMD patients usually have zero or very low levels of dystrophin, but the DMD phenotype can also result from in-frame mutations that result in a unstable transcript or dysfunctional dystrophin isoform. BMD usually results from an in-frame mutation (often an exon deletion) that affects the functional quality of the protein and also the quantity produced. It remains unclear what role protein function plays vs quantity in leading to the wide range of variability in BMD phenotypes. There are a vast number of mutations that can lead to each of these phenotypes (Tuffery-Giraud, et al., *Hum Mutat*, 30, 2009), all of which can have different effects on protein function as well as protein production. This micro-heterogeneity is common in genetic diseases and is highly germane to

evaluation of interventions targeting the gene, gene expression, or protein function. There are also non-dystrophin-related factors that can modulate phenotype.

5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.

I note that in the decades since 1988, much technical progress has been made in standardizing Western blot techniques, and the results from early studies may not be fully comparable to those from recent experiments.

- a. The seminal 1988 paper on this subject (Hoffman et al., *NEJM*, 318(21)) found that the majority of patients with DMD had undetectable levels of dystrophin using their Western blot technique and that 35 of 38 had levels below 3% in their assay. They also reported that one of seven “intermediate” patients had dystrophin levels below 3% of normal, as did one of the 18 patients with a BMD phenotype.
- b. Beggs et al., (*Am J Hum Genet*, 49, 1991) published one of the early studies on the correlation between the level of dystrophin on Western blot and clinical features of BMD. Western blot was performed using a polyclonal serum and had about a 20% variability between blots according to the authors. In this study a number of patients with BMD or intermediate phenotype (DMD/BMD) were found to have dystrophin contents that overlapped with those of the DMD patients. Of four patients included with DMD phenotype, two had less than 5% dystrophin, and two had 10%, by their assay. Of patients with BMD/DMD phenotypes, eight were found to have 10% of normal dystrophin, two had 15%, one had 50%, and one had 100%. Three BMD patients with dystrophin levels of 10% were found; two of these had relatively mild disease.
- c. Nicholson et al., (*J Med Genet*, 30, 1993) studied patients across a wide range of DMD and BMD phenotypes. They used loss of ambulation as a criterion to establish five functional groups, grouped from one (most severe, LOA before age 9) to five (LOA past age 40) (pre-steroid era). *They found a linear relationship overall between dystrophin levels (Western blot with Dy4/6D3 antibody, using myosin for a loading control) and their five categories, with more dystrophin protein translating to better function. They found no significant difference between any two adjacent groups however, which they interpreted as showing considerable overlap, as reflected in their patient level data (Appendix 1), which showed a number of less severe patients (e.g., Group 2 or 3) registering no or very low dystrophin abundance on their Western blot assay.* Of note, they reported a higher average level of dystrophin protein in severe DMD patients than other investigators, partly resulting from 5 of their 21 severe patients reported to have dystrophin protein levels above 20.
- d. Neri et al., (*Neuromuscular Disorder* 17, 2007) reported on families with X-linked Dilated Cardiomyopathy. In these families, mutations give rise to absent dystrophin in heart muscle, but only reduced levels of nearly normal dystrophin in muscle tissue. One patient in their series had a normal neurological exam at age 23, an elevated CPK, and 29% of normal dystrophin protein in skeletal muscle by Western blot. This example can contribute to understanding the role of abundance of dystrophin protein vs compromised function.

- e. Anthony et al., (*JAMA Neurology*, 71, 2014) evaluated the correlation between phenotype and mRNA and protein expression in patients with both in-frame and out-of-frame mutations amenable to exon 44 or 45 skipping. Studying a group of patients with closely related deletions could diminish variability due to differences in function of the truncated protein. Five samples from patients with clinical “mild” BMD and in-frame mutations underwent Western blot analysis using the Dys-2 antibody. Their mean protein expression was 17% (normalized to actin) with a standard deviation of 7.5%. Two of the “mild” patients had dystrophin levels in this assay of around 10%. Based on comparisons of IHC experiments with various antibodies, the authors found “*no clear correlation between the level of dystrophin transcript or protein expression with clinical severity*” in 13 patients with in-frame mutations leading to BMD. The finding of Neri et al., above, along with this report, reinforce the concept that protein function (i.e., quality) is an important determinant of clinical severity and undermine the concept that 10% dystrophin protein content is a threshold, since these patients had “mild” BMD.
- f. Van den Bergen et al., (*J Neurol Neurosurg Psychiatry*, 85, 2014) compared dystrophin levels by Western blot with clinical severity in 27 patients with a clinical diagnosis of BMD. Dystrophin expression ranged from 4-71% and 3-78%, depending on the antibody used. *The authors found no linear relationship between dystrophin expression by Western blot using newly acquired muscle biopsies and clinical severity, muscle strength, or fatty infiltration on MRI.* Although this was the case for the majority of the patients, who had dystrophin levels above 20% of normal, four patients had levels at or below 10%. These patients generally had a more severe phenotype: one patient with a dystrophin level of 10% was wheelchair dependent at 45 years; one patient with a level of 7% developed trouble with stair walking at age 21; one patient with a level of 4% had a DMD phenotype with wheelchair dependency at age 10, one patient with a level of 3% had wheelchair dependency at age 25.
- g. Anthony et al., (*Brain*, 134, 2011) studied 17 BMD patients with exon 51 or 53 skipping-amenable mutations by IHC methods. These patients primarily had very mild or asymptomatic disease; the one patient classified as severe was ambulatory at age 25 but unable to run. *There was a statistically significant difference in dystrophin expression by IHC when patients classified as mild disease were compared to asymptomatic patients.*
- h. Bello et al., (*Neurology* 87, 2016) published a detailed study of loss of ambulation in DMD patients with particular exon deletions, using the CINRG-DNHS, a prospective natural history study. They found patients with exon 44 amenable mutations to have a two-year delay in loss of ambulation compared to the overall comparison group. This finding had previously been reported by another group (van den Bergen, et al., *J Neuromuscul Dis*, 1, 2014). The mutations studied (primarily single-exon deletion of exon 45) are known to undergo spontaneous skipping with production of some dystrophin. According to the Bello report, of six patients previously tested by IHC, three showed traces of dystrophin production and 0/four (possibly other patients) had dystrophin detectable by Western blot. These authors suggest that the observed differences in loss of ambulation (LOA) could be due to small amounts of spontaneously induced dystrophin that slightly ameliorate the ordinary DMD phenotype.

- i. Cirak et al., (*Lancet*, 378, 2011) published a study (AVI-4658) using intravenously administered eteplirsen that showed a detectable increase in dystrophin protein levels using both Western blot and immunofluorescence in 3/19 patients. The authors reported that the functional properties of restored dystrophin were confirmed by assessing increased levels and co-localization of neuronal nitric oxide synthase (nNOS) and sarcoglycan with dystrophin. Such a protein assembly is suggested to be indicative of functional restoration of the dystrophin-associated glycoprotein complex in muscle fibers (Molza et al., *JBC*, 290, 2015; Wells KE et al., *Neuromuscul Disord*, 2003). Cirak et al., reported that the restoration was more so in patients with exon 49-50 deletions than in those with 45-50 deletions, which is consistent with a previous observation that nNOS binding domain is located in dystrophin exons 42-45 (Lai Y et al., *J Clin Invest*, 2009). These studies suggest that important functional domains are included in the dystrophin protein induced by eteplirsen.

To summarize what is known about the association between dystrophin levels and phenotype, dystrophin content above about 10% on Western blot is usually associated with a BMD phenotype, except in patients with higher levels of dystrophin (including above 50%) who potentially have functionally deficient protein leading to a DMD phenotype. Within the BMD phenotype, a proportional inverse relationship between disease severity and protein expression has not generally been demonstrated (i.e., between 10-100%), although there may be a broad association, as seen in the Anthony study (*Brain*, 134, 2011). This may be due to the fact that protein quality, rather than quantity, plays a key role in determining phenotype in BMD. Patients with DMD are usually found to have no detectable, or very low levels of, dystrophin. Dystrophin content in the 3-10% range has been associated with DMD, DMD/BMD, and BMD phenotypes. I find no evidence of a threshold value for protein content and expression of a DMD phenotype, although the majority of DMD patients reported in the literature have dystrophin that is undetectable by the Western blot assays used. Generally, the divide between DMD and BMD, in terms of protein, is the result of the consequences of an OOF or an in-frame mutation, respectively. I believe that the conventional threshold, at or below 10% protein, was derived from the IHC data that seem to estimate low-level protein content about 10% percentage points higher on IHC than on Western blot, so that the majority of DMD patients would read out at 10% of normal dystrophin on IHC. I believe that evidence from Western blot and other experiments discussed above show that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

These findings are germane to the determination of “reasonably likely to predict clinical benefit.” The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.

Additional support for “reasonably likely” comes from the long-term experience with the drug. The sponsor’s comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of non-randomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.

Several facts militate against this conclusion. First, one of the exon 52 deletion trial subjects (subject 6) had a fairly low score on the 6MWT at entry and a very low score on the NSAA, compared to other subject around his age. He also was the only subject in the trial noted to be unable to rise without external support at baseline. Additionally, the Italian external cohort had exon 52 deletion representation.

Questions have been raised about the correlation of dystrophin levels from Western blot with clinical outcomes. The 6 Minute Walk Test does not show a strong correlation. I evaluated the NSAA in children who could still walk (because the NSAA primarily scores activities related to walking) and who also had a dystrophin result at 180 weeks (Table 1). I did this because the NSAA includes multiple measures and therefore might have some noise averaged out. I looked at the absolute decline in NSAA in patients since study initiation, and did not correct for the initial time some patients spent on placebo. I only evaluated patients who were ambulatory. There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1) This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.” In totality, I find that the comparative disease course data provide additional support for the use of the surrogate endpoint of an increase in dystrophin expression as “reasonably likely to predict clinical benefit.”

Therefore, both the biochemical data and the clinical data lead me to conclude that an “increase in dystrophin production” is reasonably likely to predict clinical benefit in DMD.

CONFIRMATORY TRIALS

The sponsor is currently conducting a nonrandomized, concurrently controlled trial in patients with mutations amenable to exon 51 skipping compared to untreated DMD patients with other exon deletions. Because of the relatively low level of protein induced, additional doses should be aggressively pursued and, if successful, a dose-comparison trial could be confirmatory. The sponsor has also planned to initiate a randomized trial with a related compound in other exons. The clinical results from these trials can inform the predictive value of the surrogate endpoint.

EXPLORATION OF ADDITIONAL DOSES, REGIMENS, AND DRUG-MUTATION INTERACTION

The dystrophin levels achieved in this development program are well below those initially hoped for. I agree with Dr. Farkas and other reviewers that the sponsor should aggressively explore higher doses or more frequent administration of eteplirsen. It appears that this is possible given the toxicology data and the clinical safety profile observed to date.

Because patients in the Sarepta 180 week cohort had a range of deletions in the dystrophin gene, variability in the pharmacodynamic response among deletions is of great interest. The two patients with over 2% dystrophin in the 180 week Western blot both had exon 52 deletions. These patients also fared fairly well, clinically. This raises the question of whether patients with this exon deletion naturally produce more dystrophin. One of these subjects had a baseline sample available. It was found to be below the limit of quantitation. There was an exon 52 subject included in the added baseline controls. This subject's assay had replicate results of 0.3% and below the limit of quantification, respectively, as discussed above. This suggests that baseline dystrophin levels are not higher in exon 52 deletion subjects and that there may be a drug-deletion interaction, wherein subjects with this deletion may have a more robust pharmacodynamic response to the drug. There were a number of apparent non-responders to the drug. It will be important to find out if this is mutation specific. It is likely that more detailed knowledge about each patient's specific mutation will have to be generated to study this in detail.

COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

The development program for eteplirsen was seriously deficient in a number of respects that may have led to delay in broad access and certainly led to difficulties in regulatory review. In my assessment, the most egregious flaw was the lack of robust and high-quality assays early in the development program. Inaccurate conclusions from the assays used led to a flawed development program. Additionally, the entire drug development field must recognize that there is no such thing as an "exploratory study" for a serious, life-threatening illness without therapeutic options. Randomization should be performed very early in the development program, and open-label studies should be avoided. When possible, seamless adaptive dose-finding and early efficacy studies should be carried out with the goal of most efficiently generating the data needed to demonstrate safety and effectiveness.

The flaws in the eteplirsen development program led to severe challenges in regulatory review. 21 CFR 312.80, concerning drugs intended to treat life-threatening or severely-debilitating illness, states that FDA has determined "that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness...Physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would accept from products that treat less serious illnesses." I note that the acceptable risks include greater uncertainty about the effects of the drug. The Peripheral and Central Nervous System Drugs Advisory Committee met on this application on April 25, 2016. There was a split vote (7 against, 6 for) on the question of accelerated approval for this drug, reflecting the greater than usual uncertainty about the application. This vote was taken before the additional data on protein expression were submitted.

To conclude, the studies used in this analysis to support the effect of eteplirsen on dystrophin were adequate and well-controlled as specified in 314.126. In addition, the surrogate of increased dystrophin production is reasonably likely to predict clinical benefit. Given the deficiencies that have been identified in the development program, my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk. In addition, adequate confirmatory studies are underway and planned and are capable of further refining our understanding of the biomarker and providing evidence about the nature of the clinical benefit. The approval does not create any risk of compromising the confirmatory trials because of their nature. Therefore, I find that the probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.

Table 1 Patient Data on Change from Baseline in 6MWT and NSAA

180 Weeks
Change from
Baseline

Subject	Baseline WB	180 Week WB	Fiber Intensity	PDPF	Δ 6MW	Δ NSAA
002	N/A	0.14	MD	4.54	-67	-14
003	N/A	0	7	1.42	-174	-27
004	N/A	0.96	28	29	-168	-17
005	0	N/A	N/A	N/A	-231	-19
006	N/A	2.47	29	21	-23	-3
007	N/A	0	12	7	-197	-19
008	N/A	0.98	26	12	-291	-17
009	N/A	0.52	23	22	0	0
010	N/A	1.62	21	24	0	0
012	N/A	0.38	26	33	-114	-19
013	0	1.15	32	19	-170	-16
015	0	2.05	30	18	-1	-13

Data from Sarepta Therapeutics, Inc. PCNSD Advisory Committee Briefing Document, Appendix 5, p. 149 (6MW and NSAAO Appendix 11, p. 155, (Percent Positive Dystrophin Fibers (PPDF), Appendix 12 p. 156 (fiber intensity) 14, p. 159. (Western blot),

Figure 1. Decline in NSAA by % Dystrophin on Western blot

