

From: [Kojak, Michelle](#)
To: [Woodcock, Janet](#)
Cc: [Shreeve, Chris](#)
Subject: Eteplirsen media coverage
Date: Friday, November 04, 2016 3:17:58 PM

Good afternoon Dr. Woodcock,

Below please see some recent media coverage on eteplirsen you may want to read before your Biopharma discussion this afternoon. I believe you've already seen the one from Politico, but I included it for reference at the end.

Michelle

Pink Sheet

Sarepta Pressured FDA On Eteplirsen Due To 'Dire' Finances, Gave Investors Rosier Picture

03 Nov 2016

Executive Summary

Emails reveal company wanted timelines and approval commitments from FDA towards the end of the eteplirsen review, saying it might not be able continue studies; at the same time, Sarepta was telling investors it had 12 months of cash on hand.

[Sarepta Therapeutics Inc.](#), tried using company financial problems to push FDA to complete the final stages of the review of the Duchenne muscular dystrophy drug *Exondys 51* while also telling investors there was enough operating capital to continue for a year.

The move did not work because FDA's approval was delayed several months after officials appealed the final decision made by Center for Drug Evaluation and Research Director Janet Woodcock. But the emails exchanged between FDA and Sarepta officials could partially explain why the company's financial health, which the agency normally would not consider, became an issue in the decision to approve the product.

[Emails, memos and other documents](#) related to the review of Exondys 51 (eteplirsen) indicate that in June, after FDA asked for additional dystrophin data from Sarepta, the company requested that the process be started quickly. Sarepta also asked FDA to confirm that the drug would be approved by the end of that month once the required increase in dystrophin was shown.

Shamim Ruff, Sarepta senior vice president of regulatory affairs and quality, wrote in a June 2 email that the company could complete the requested additional biopsies and dystrophin analysis by the end of that month, assuming the process goes perfectly the first time, but the process had to begin by June 6.

"There is no room for flexibility with this date due to our dire financial constraints as a result of the ongoing delays," Ruff said.

The original review goal for the product was Feb. 26, but it was moved to May 26 after Sarepta submitted additional data following release of FDA's advisory committee materials. (Also see "[Sarepta's Duchenne Treatment Likely Making Progress At FDA](#)" - Pink Sheet, 8 Feb, 2016.)

FDA also missed that deadline in asking for more dystrophin data after the advisory committee meeting.

Delays Could Impact Study Completion

The message did not provide more detail on the company's financial issues that were referenced.

Later in the email, Ruff also asked that "FDA will confirm – by June 3, in writing, that accelerated approval will be granted by the end of June when an increase in dystrophin is demonstrated ..."

She also said that further delays could impact the company's ability to complete the clinical studies for Exondys 51.

"Labeling discussions and post-marketing commitments to be conducted concurrently and completed by the end of June or sooner," Ruff wrote. "Any delay, for any reason, past June will significantly impact our ability to continue the ongoing eteplirsen studies."

It would appear that Ruff's comments resonated with Woodcock.

Woodcock sent a "General Advice" memo to the company dated June 3 that said if the analysis of the new biopsies showed a meaningful increase in dystrophin using Western blot analysis, "we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable)."

She also asked that Sarepta refrain from publically communicating "specific details of this plan until after completion in order to allow maximum procedural efficiency."

The company's attempt to speed the approval did not materialize.

FDA did not announce Exondys 51's approval for treatment of Duchenne in patients amenable to exon 51 skipping until Sept. 19. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

The product launched immediately after the approval, which included post-marketing confirmatory trials. (Also see "[Sarepta Must Balance Exondys 51 Confirmatory Trials And Sales](#)" - Scrip, 23 Sep, 2016.)

The disagreement between FDA staff lead to a formal appeal process that eventually reached Commissioner Robert Califf.

Exondys Approval: FDA Commissioner's Draft Decision Drew Internal Rebuke

By [Sue Sutter](#) 03 Nov 2016

Even at the final step, FDA's review of Sarepta's Duchenne muscular dystrophy drug remained collaborative and contentious, as Commissioner Califf's view that accelerated approval would not set a new precedent drew pushback from ODE Director Unger, while Acting Chief Scientist Borio said the draft decision downplayed the 'miniscule' amount of dystrophin with eteplirsen.

[Read the full article here.](#)

As part of that process, Woodcock suggested that Exondys 51 may need to be approved for Sarepta's financial health and to promote drug development in Duchenne.

Califf said he was troubled by the comments. (Also see "[Woodcock's Consideration of Sarepta Financial Issue Raises Eyebrows](#)" - Pink Sheet, 19 Sep, 2016.) But he deferred to Woodcock's judgement, in part because he did not want a political appointee affecting the approval process. (Also see "[Political Appointees Shouldn't Influence Approval Decisions, Califf Says](#)" - Pink Sheet, 20 Oct, 2016.)

Company About To Raise Money At Same Time

Ruff's statement about Sarepta's financial problems does not appear to entirely agree with the company's statements to investors at that time.

Sarepta's quarterly report filed with the SEC for the period ended March 31 stated that while the company had not generated any revenue from product sales to date, it had enough resources to fund its current operational plan for another 12 months.

Its SEC filing for the first half of 2016, which ended June 31, included a similar statement that its cash, cash equivalents and investments were sufficient to fund the operational plan for "at least" the next 12 months.

And about a week after Ruff's email (June 8), the company announced it was raising another \$37.5m before expenses through a stock sale, which was completed later that month.

Proceeds were to be used "principally for product and commercial development, manufacturing, any business development activities and other general corporate purposes," according to the press release.

Sarepta did not respond to a request for comment on the differing views in the email and SEC filings.

Ruff's June 2 message to Woodcock followed a teleconference that morning. Sarepta requested the meeting with Woodcock and Richard Moscicki, CDER deputy center director for science operations, because it could not meet the dystrophin data request "in a timely manner."

"Please note that even if a protocol amendment is not required, it would take us several months to analyze the PROMOV1 samples," Ruff wrote in a June 1 email.

FDA questioned the methods used to gather and analyze muscle biopsies to show Exondys 51 induced dystrophin production. Reviewers also raised a number of concerns about whether the amount of dystrophin that Exondys 51 produced was in fact significant and whether the boys in the clinical trials were improving. (Also see "[Duchenne Muscular Dystrophy: Second Product Isn't The Charm](#)" - Pink Sheet, 15 Jan, 2016.)

After an advisory committee voted against recommending approval, the agency requested more biopsies from the ongoing PROMOV1 trial. (Also see "[Priority Review Politics, With Two Pending DMD Products, FDA Still Faces Community Anxiety](#)" - Pink Sheet, 18 Aug, 2016.)

SEC Wants Docs From Exondys 51 Competitor

In the wake of the approval, a number of FDA officials, including Woodcock, have warned against trying to repeat the development model Sarepta used.

FDA said the approval involved the maximum amount of flexibility allowed. (Also see "[No More Sarepta-Like Development, FDA Officials Say](#)" - Pink Sheet, 20 Oct, 2016.)

Califf also has said he wants to better outline FDA's interpretation of the accelerated approval regulations to increase sponsor and public understanding. (Also see "[Accelerated Approval Should Be Less 'Wide Open,' Califf Says](#)" - Pink Sheet, 20 Oct, 2016.)

But one investor has said that his firm already is receiving pitches for development programs similar to Exondys 51. (Also see "[FDA's Fears Realized: Sponsors Pitching Investors: 'Sarepta Model'](#)" - Pink Sheet, 25 Oct, 2016.)

Sponsors of other Duchenne drugs that have not fared well with FDA also are appealing or considering appealing the decisions. (Also see "[Sarepta's Shadow: BioMarin Mulls Turning The Extraordinary Into A Template](#)" - Pink Sheet, 15 Oct, 2016.)

BioMarin Pharmaceutical Inc., which received a complete response letter after review of its proposed Duchenne product drisapersen, also is dealing with an SEC subpoena related to the product.

The company's Nov. 3 quarterly SEC filing stated that the SEC is seeking documents "in connection with a non-public, fact-finding inquiry related to its former drisapersen program." BioMarin also stated that the letter accompanying the subpoena says that the action is not an indication the company broke the law.

The company intends to cooperate fully with the investigation, according to the filing.

Medscape

Duchenne Drug Approval Still Leaves Bad Taste for Many

Alicia Ault

November 03, 2016

The September approval of a therapy for Duchenne muscular dystrophy (DMD) continues to rankle many who say the evidence did not support it and that it may set a dangerous precedent at the agency, although specialists who work in the field say they are pleased to finally have an option for patients.

The latest critique came in the form of a viewpoint [published online](#) in *JAMA* on October 24.

The manufacturer's development program for eteplirsen (*Exondys 51*, Sarepta Therapeutics) "has provided a worrisome model for the next generation of molecularly targeted therapies: demonstrate a slight difference in a laboratory test, activate the patient community, win approval, and charge high prices, while relying on limited regulatory follow-up," write Aaron S. Kesselheim, MD, JD, MPH, and Jerry Avorn, MD, both from the Pharmacoeconomics and Pharmacoeconomics Department at Brigham and Women's Hospital, Boston, Massachusetts.

But Kathryn Wagner, MD, PhD, director of the Center for Genetic Muscle Disorders at the Kennedy Krieger Institute, Baltimore, Maryland, said she's pleased the drug was approved. "I want the option to be able to provide Exondys 51 to my patients," she told *Medscape Medical News*.

Thomas Vidic, MD, a clinical neurologist and medical director at Indiana Medical Research, LLC, agrees. "I'm happy for the very narrow window of patients who are appropriate to have access to the drug," he said.

However, Dr Vidic added, "We have to approach this drug with discretion because it's going to be expensive." Sarepta has said it will charge \$300,000 a year for eteplirsen.

And as pleased as he is to have something to offer the small number of patients with DMD who might benefit, said Dr Vidic, "unfortunately, the results from the trial are not as dramatic as we would like to see."

It's estimated that only 9000 to 12,000 patients have DMD in the United States, and the mechanism of action for this treatment applies to only about 13% of patients, those with mutations of the dystrophin gene amenable to exon 51 skipping.

The US Food and Drug Administration (FDA) official who ultimately approved eteplirsen, Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, said Sarepta's program was fraught with mistakes. Among them: "problems with the assays, the failure to randomize patients...a very short randomized trial," said Dr Woodcock, in an interview with *Medscape Medical News*.

Sarepta did provide a validated assay for dystrophin, the surrogate marker used to judge eteplirsen's effectiveness, but that assay was not instituted until after the development program was over. Dr Woodcock said.

"That's not ideal, either," she said. "But they did present that evidence at the end of the day."

Divisions Persist Within FDA

In her opinion, "the approval is a scientific decision," but one that required the maximum regulatory flexibility allowed under the accelerated approval law.

The agency officials who led the eteplirsen review objected so strongly to the approval in fact, that they asked FDA Commissioner Robert Califf, MD, to examine Dr Woodcock's decision. The appeal was brought forward by Ellis Unger, MD, director of the Office of Drug Evaluation I at CDER, and sent to the Commissioner by Luciana Borio, MD, chair of the Agency Scientific Dispute Process Review Board.

Although the review board found no procedural basis for Dr Unger's appeal, Dr Borio agreed with him that there were not sufficient data to support accelerated approval for eteplirsen, and asked that Dr Califf either review the approval or strike a panel of experts to do so.

Dr Califf elected to review the approval himself. The examination took months, culminating in a [126-page memo](#) in which the commissioner outlined why he supported Dr Woodcock's final decision. The memo was dated September 16 but not made public until after the [approval was announced](#) on September 19.

"My decision following this review is to defer to Dr Woodcock's judgement and authority to make the decision to approve eteplirsen under the accelerated approval pathway, in her capacity as Director of the Center for Drug Evaluation and Research," Dr Califf writes.

The parties disagreed about what might be the expected clinical effect of the level of dystrophin produced by eteplirsen in the studies, he noted, but pointed out that "qualified experts with extensive experience in FDA decision-making and stellar track records can assimilate the same scientific evidence and disagree about the extrapolation to whether the evidence supports a conclusion that the treatment has an effect that is 'reasonably likely' to predict clinical benefit.

"Given that I do not have technical expertise beyond those already involved in this decision and the record contains adequate evidence to support her conclusion, I defer to the judgement of the Center Director to approve eteplirsen under accelerate approval with the stipulations delineated in her Decisional Memo," Dr Califf concluded.

Many of Dr Woodcock's colleagues still disagree with her having used such regulatory flexibility in this case. At an October meeting of the National Organization for Rare Disorders (NORD) in Washington, John Jenkins, MD, director of the FDA's Office of New Drugs, told attendees that he did not support approval, as he saw multiple failures in Sarepta's development program.

These included a failure to validate the dystrophin biomarker, a lack of early randomization, and difficulty reconciling patient and family reports of improvement in function when the trial data showed otherwise, said Dr Jenkins.

He suggested the company had also erred in failing to make timely reports of early findings. Instead, Sarepta relied on post hoc analyses, which Dr Jenkins called "wrong, fundamentally." Such analyses "are generally hypothesis-generating exercises and should lead to a new clinical trial, not the basis for regulatory approval," Dr Jenkins said.

At the same NORD meeting, Dr Califf expanded on the rationale for his support of Dr Woodcock. It was, in part, a way of safeguarding the FDA from outside interference, a category that he said included him, since he is a political appointee.

"Setting a precedent of political appointees intervening in decisions that belong in a scientific process would risk opening the door to a potentially dangerous temptation for others, including political appointees within government and other non-FDA groups to intervene more frequently," he said.

FDA decision making is "difficult and imperfect," Dr Califf said, but allowing "political meddling would undermine confidence and introduce the kind of bias that's not helpful."

Meddling or Proper Influence?

Some critics say the eteplirsen approval was the result of just such outside meddling — in particular from patient advocacy groups who held multiple meetings with the FDA during the drug's development and who also showed up in force at the April 2016 advisory committee meeting.

But Pat Furlong, president and CEO of Parent Project Muscular Dystrophy (PPMD), a Hackensack, New Jersey-based nonprofit group, is proud of her organization's influence. "I think the pressure made a difference," Furlong told *Medscape Medical News*.

She believes it's time for "a new social contract," one that brings patients, the FDA, and drug developers closer together as collaborators. That's not such a wild idea: The FDA, by law, is required to work more closely with patients.

PPMD is at the leading edge. It began meeting with the FDA in 2008 to discuss unmet needs in the DMD area, along with benefits and risks of therapies in development, among other topics. Ultimately, PPMD paid a consultant to help establish guidance on development of DMD therapeutics, which the agency used as the basis for the guidance it issued, Furlong said.

PPMD is primarily funded by families, but it receives some money from industry to support its conferences and meetings, she said.

The organization is "thrilled with this approval," said Furlong, adding, "clinicians in the neuromuscular community are going to embrace this drug."

She acknowledged that cost could be a barrier. "It would be very few families that could afford that price if they were paying out of pocket," said Furlong. But she expects many patients to have insurance coverage or assistance from Sarepta.

Cigna and Blue Shield have agreed to cover eteplirsen, but one of the nation's biggest insurers, Anthem, will not, [calling the drug investigational](#).

"Cost is a major concern," not just for families, but also to society, said Dr Wagner. She will be recommending the drug "to boys who are amenable to skipping exon 51" but still expects to need to manage expectations, she said. "I will inform the families that the drug may reduce the rate of decline but is unlikely to make the boys stronger," she added.

Dr Vidic sees a narrow window of usefulness. "Once there's too much damage, I don't think it's really going to be helping the patients," he said. He doesn't want it used by clinicians outside of the neuromuscular community and said he hopes "that parents with children with advanced disease don't pressure their doctor into prescribing it."

The safety and effectiveness of eteplirsen should continue to be closely monitored, and, preferably, a registry should be established, Dr Vidic said.

Furlong and both physicians said they're looking to the confirmatory study to provide more guidance. The FDA required Sarepta to determine whether eteplirsen truly improves motor function — something that was only suggested, not confirmed, by the data used for approval. If that benefit is not confirmed, the agency can take the drug off the market.

If that happens, "that will be a sad day," said Dr Wagner.

Critics Warn of Precedent

One of the more outspoken critics of the approval has been Diana Zuckerman, PhD, president of the National Center for Health Research, a Washington, DC-based nonprofit education and advocacy group.

Dr Zuckerman's organization testified against approval at the advisory committee meeting, believing the data did not demonstrate effectiveness. The group is concerned that now that eteplirsen is available, Sarepta will not be able to recruit controls for the confirmatory study, Dr Zuckerman told *Medscape Medical News*.

"You may only get people who are too poor to afford the drug, and their insurance doesn't cover it," she said. If only those who can't get the drug otherwise are the controls, "that's so unethical on every level," said Dr Zuckerman.

In her mind, the FDA allowed patient advocates to "undermine the scientific integrity of the process," she said. Dr Woodcock "was clearly moved by these kids," said Dr Zuckerman.

"We're not opposed to the paradigm shift of including patient voices," she said. "We just think the patient voices should help improve study designs and make sure that the outcome measures are the ones that matter to patients."

She contends a rise in the dystrophin was irrelevant if patients did not actually have improved walking ability or other measures crucial in day-to-day life.

Dr Zuckerman also said she's concerned the eteplirsen approval will set a bad precedent by encouraging industry to skimp on doing the hard science if approvals can be won more easily by bringing external pressure to bear.

Conversely, Ira Loss, a long-time FDA-watcher and an investment adviser with Washington Analysis, sees it differently. Because of the eteplirsen approval, "there are all these companies that are encouraged to do work in Duchenne muscular dystrophy," he told *Medscape Medical News*.

He pointed to recent collaborations Sarepta struck with Spectrum Pharmaceuticals and another company in the muscular dystrophy field. In addition, two other companies have submitted DMD therapies to the agency recently, he said.

Loss said the eteplirsen situation is similar to when the first drug for HIV was approved. People with AIDS had been pushing the FDA hard to get any therapy out to market. AZT, the first to reach the agency, was extremely toxic and not so effective. But in 1987, the FDA approved the drug, with just one trial that had been stopped early because of a high number of placebo deaths.

Within 3 years, there were better therapies, said Loss. "But it was getting the first one out there that got everyone else involved," he said.

Furlong, the patient advocate, said her organization had learned from the HIV community and had even consulted with ACT-UP, the group that was most associated with pressing the FDA in the 1980s and 1990s.

She thinks the eteplirsen approval "has galvanized the industry to say 'I can do it better, faster.'"

However, FDA officials are insistent that Sarepta's development program is not a good model to follow and that the approval process for eteplirsen won't become the modus operandi.

"I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of the data and information," said Dr Califf (page 12 of his [memo](#)) in reviewing the decision.

For her part, Dr Woodcock seems glad to put it behind her. "We hope we won't see a development program like that again," she said.

Nov. 3

Executive Summary

Even at the final step, FDA's review of Sarepta's Duchenne muscular dystrophy drug remained collaborative and contentious, as Commissioner Califf's view that accelerated approval would not set a new precedent drew pushback from ODE I Director Unger, while Acting Chief Scientist Borio said the draft decision downplayed the 'miniscule' amount of dystrophin with eteplirsen.

FDA officials involved in the dispute over whether to approve **Sarepta Therapeutics Inc.'s Exondys 51** (eteplirsen) did not hold back their criticisms when FDA Commissioner Robert Califf circulated his draft decision supporting accelerated approval for the Duchenne muscular dystrophy drug.

Office of Drug Evaluation I Director Ellis Unger questioned Califf's conclusion that Center for Drug Evaluation and Research Director Janet Woodcock had considered all relevant scientific evidence in deciding to grant accelerated approval. Unger further disagreed with Califf's view that the decision to approve eteplirsen would not set a precedent and lower the standards for accelerated approval.

Granting accelerated approval to drugs that show "a mere scintilla" of an effect on a surrogate endpoint is an approach that "should receive broader public (and FDA) input before being implemented." – ODE I Director Unger.

"Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for rare neurological disorders. Ellis wrote in a Sept. 14 email to Califf. "But in my opinion, this approach should receive broader public (and FDA) input before being implemented."

Separately, Acting Chief Scientist Luciana Borio said Califf's draft memo seemed to "downplay the significance of the very small amount of dystrophin reported in the eteplirsen NDA."

The Unger and Borio emails, along with other review documents, provide a deeper look at how the dissension over eteplirsen's approvability reached the highest ranks within FDA.

Among the newly released documents are emails between FDA and Sarepta, including one in which the company asserted it was facing "dire financial constraints" due to review delays and demanded written assurance from top CDER staff that accelerated approval would be forthcoming if data from an ongoing study showed an increase in dystrophin. (Also see "**Sarepta Pressured FDA On Eteplirsen Due To 'Dire' Finances, Gave Investors Rosier Picture**" - Pink Sheet, 3 Nov, 2016.)

Dispute Goes To The Commissioner

FDA granted accelerated approval Sept. 19 to Sarepta's antisense oligonucleotide for treatment of patients who have a confirmed mutation of the Duchenne muscular dystrophy (DMD) gene that is amenable to exon 51 skipping. The decision to approve was made by Woodcock over the objections of the Division of Neurology Products review team, other review disciplines and some high-ranking CDER officials. (Also see "**Sarepta's Eteplirsen Approved After Contentious Internal Debate**" - Pink Sheet, 19 Sep, 2016.)

Unger, who heads the office that oversees the neurology review division, submitted a scientific dispute resolution appeal challenging Woodcock's decision. Unger and Woodcock disagreed as to whether the quantity of dystrophin produced by eteplirsen in clinical trials is an effect that is "reasonably likely" to predict clinical benefit, such that it can serve as a surrogate endpoint supporting accelerated approval.

Unger said that although there was evidence from interim data in ongoing Study 301 that eteplirsen induces dystrophin production in muscle cells, the effect size was inadequate, with a mean increase of 0.3% and a range of 0-1.3%. Rather, dystrophin levels of 10% or more would be needed to affect the clinical course of DMD, the ODE I director concluded.

Woodcock rejected the idea of a minimum 10% threshold and said Western blot analyses of Study 301 results clearly showed that the drug increased dystrophin production in some patients.

Unger's appeal went first to the agency's Scientific Dispute Process Review Board, which is chaired by Borio, and then to Califf.

In his Sept. 16 final decisional memo, Califf deferred to Woodcock's judgment and authority on accelerated approval. The commissioner said he lacked the technical expertise beyond those individuals already involved in the decision and the record contained adequate evidence to support Woodcock's conclusion.

In a recent speech, Califf said career scientific staff at the agency, not political appointees like himself, should make such approval decisions. (Also see "**Political Appointees Shouldn't Influence Approval Decisions, Califf Says**" - Pink Sheet, 20 Oct, 2016.)

Unger Finds Fault With Conclusions On Process ...

On Sept. 13, Califf sent his draft decision to Woodcock, Unger, Borio and Office of New Drugs Director John Jenkins, requesting they advise him of any "significant factual errors" by close of business the following day.

In his email accompanying the draft, Califf said he had concluded that all applicable processes and procedures were followed in the decision-making on the drug's approval, the appealing parties had ample opportunity to present their views, and the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

Commissioner Califf asked agency officials to identify any "significant factual errors" in his draft decision.

Unger, however, begged to differ.

"I have concerns with respect to two areas of your memo," Unger told Califf in a Sept. 14 email.

"First, whether proper procedures were followed such that all evidence and analyses were reviewed by the center director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the center director, as was clearly the case here," Unger said.

Woodcock had made up her mind on accelerated approval before Unger, the signatory authority for the application, had completed his review, he noted.

Unger said that in drafting his complete response memorandum he took note of "ambiguities and discrepancies" in the immunohistochemistry results from

Study 201/202, the exploratory Phase I/II study that served as the basis for the NDA submission.

"I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers," Unger said. "For the three patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, advisory committee meeting."

"This discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16," Unger continued. "Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol."

Sarepta's inability to reproduce its own findings with respect to the immunohistochemistry analyses "raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in the literature," Unger said.

Furthermore, Sarepta had stated at the advisory committee meeting that it would be inappropriate to compare the firm's data from Western blot analyses to that reported in the literature "due to significant methodological differences."

"Therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is 'reasonably likely' to predict clinical benefit," Unger said. "There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program."

The regulatory record should reflect that there was "no scientific basis underlying the conclusion of 'reasonably likely' in this case. This was simply a judgment call by Dr. Woodcock," Unger said. The CDER director "might have also taken the position that, in this desperate patient population, any dystrophin production would suffice as a basis for accelerated approval, but she didn't state this."

... And Precedent

Unger also took issue with Califf's conclusion in the draft memo that eteplirsen is a "unique situation that will not set a general precedent" for accelerated approval. (Also see "[Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?](#)" - Pink Sheet, 20 Sep. 2016.)

"We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann-Pick disease, Pelizaeus-Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy," Unger said.

"Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn't apply for these diseases," he said.

In Unger's view, Califf's draft memo seemed to suggest that the reasonably likely standard for accelerated approval need not include any type of quantitative component.

"We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the 'reasonably likely' test," he said.

Borio: Focus On 'Crux' Of Disagreement

Borio, who shared Unger's view on the underlying scientific matters, also took issue with Califf's failure to address the small amount of dystrophin production seen in the eteplirsen trials.

"Your draft decisional memo never once cites the 0.3% increase in dystrophin production shown by Study 301 (or the 0.93% detected in Studies 201/202)," Borio said in a Sept. 14 email to Califf.

The draft attributed the scientific disagreement to a lack of consensus on the appropriate threshold for clinical benefit, both within CDER and in the scientific literature, as well as to concerns about the correlation between dystrophin production and clinical outcomes in Study 201/202, Borio said.

Acting Chief Scientist Borio raised concerns that the draft decision downplayed "the significance of the very small amount of dystrophin reported in the eteplirsen NDA."

"To me, the crux of the disagreement is not whether there is an appropriate threshold, but whether such a minuscule amount of dystrophin is reasonably likely to predict clinical benefit," she said. "Your draft decisional memo does not address that issue. In my view, it is not sufficient to say that no threshold has been established and that, therefore, any increase in dystrophin production is reasonably likely to predict clinical benefit."

Although FDA declined to provide Califf's draft memo, it appears the commissioner did take Borio's suggestions into consideration in writing the final version.

The final memo notes that the key points of disagreement were whether the amount of dystrophin produced is sufficient to be reasonably likely to predict a clinical benefit. It also reflects Unger's view favoring a 10% threshold, and Woodcock's position that FDA should exercise its greatest flexibility possible while remaining within its statutory framework.

Fierce Biotech

Sarepta bemoaned 'dire' financial situation as it pushed for Exondys decision

by Ben Adams |

Nov 4, 2016 6:05am

The documents keep coming from the FDA over the controversial September decision to approve Sarepta's (\$SRPT) Duchenne med Exondys 51 (eteplirsen), and this week amid 311 pages of fresh docs, we saw the pressure the biotech was under, and how this pressure was pushed onto the FDA to make a decision on the med.

In an email dated June 2 of this year from Sarepta's head of regulatory affairs Shamim Ruff to the FDA's Dr. Janet Woodcock and Dr. Richard Moscicki, Ruff said that, in order to grant the FDA's request to produce new dystrophin analysis for its med, the FDA would have to agree that the process must start by June 6: "There is no room for flexibility with this date due to our dire financial constraints as a result of the ongoing delays."

It also told the regulator, with the bold and underlining direct from the email: "FDA will confirm--by June 3, in writing, that Accelerated Approval will be granted by the end of

June when an increase in dystrophin is demonstrated based on the assumptions above.”

In [redacted documents](#) released along with the approval back in September, it became clear that it was Dr. Woodcock who helped push the drug through to approval—despite internal protestations from Dr. Ellis Unger, a senior doc at the agency, to FDA Commissioner Dr. Robert Califf.

Dr. Unger, among others, had expressed concerns at the small study and its lack of clear efficacy, but Dr. Woodcock said the FDA must be “prepared to be flexible with respect to a devastating illness with no treatment options.”

The email from Sarepta about its “dire financial constraints” clearly had an impact on Dr. Woodcock, who said that Sarepta in particular “needed to be capitalized” and noted that the biotech’s stock had risen and fallen on a series of updates over the year.

In these documents, it recorded: “Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would ‘lapse into a position of’ self-treatment.”

Dr. Califf said he would “defer” to Dr. Woodcock in this case and allow the green light.

In the latest tranche of emails from the FDA, more details of Dr. Unger’s protestations have also come to light. In an email dated Sept. 13, Dr. Califf sent a memo explaining that he would not overrule Dr. Woodcock’s wish for the drug to gain approval.

Dr. Unger said in reply that he had several “concerns” with the memo: “First, whether proper procedures were followed such that all evidence and analyses were reviewed by the Center Director before a decision was rendered, and second, whether this decision will set a general precedent—where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the Center Director, as was clearly the case here.”

Dr. Unger said that in the case of this drug, he did not feel that “All applicable processes and procedures were not followed; I did not have the opportunity to present this highly relevant scientific evidence to Dr. Woodcock; and Dr. Woodcock’s decision to grant accelerated approval was made prior to consideration of all relevant scientific evidence.”

He said “there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is ‘reasonably likely to predict clinical benefit.’”

“Unaware of my final conclusions on this matter, Dr. Woodcock did not rebut the above reasoning. As I noted (and the SDR Board appeared to agree), she provided no cogent rationale for her decision that the barely detectable amount of dystrophin produced is ‘reasonably likely to predict clinical benefit.’”

“Dr. Woodcock told the SDR Board that her decision was based on her 30 years of experience at FDA and her own “medical/scientific judgment.” (SDR Board Memo, page 16). I think it will be important for the regulatory record to reflect that there was no scientific basis underlying the conclusion of ‘reasonably likely’ in this case. This was simply a judgment call by Dr. Woodcock.”

Dr. Unger also questioned why DMD should get a special pass: “We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann–Pick disease, Pelizaeus–Merzbacher disease, Pompe disease, Sandhoff disease, and Xlinked adrenoleukodystrophy.

“Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn’t apply for these diseases.”

He concluded: “Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for these disorders. But in my opinion, this approach should receive broader public (and FDA) input before being implemented.”

A number of FDA experts have in the weeks after its approval come out against the drug’s approval. John Jenkins, who runs the FDA’s office for new meds, spelled out his problems with the approval in a presentation last month, saying that the “path taken by Sarepta NOT a good model for other development programs.”

This was followed by the external FDA expert Aaron Kesselheim, who advised against the regulator approving Exondys 51, used a [JAMA article](#) to hit out at the regulator’s processes and the biotech that led to its green light.

Politico

EYE ON FDA

Newly released documents reveal internal frustration with Califf over Sarepta. Top drug reviewers challenged Commissioner Robert Califf’s decision to side with drug center director Janet Woodcock, who overruled her staff and approved Sarepta’s Duchenne muscular dystrophy treatment in September.

That’s according to a 300-page trove of FDA documents made public on Thursday night, with questions still simmering about the [controversial decision](#) and critics pointing to the lack of evidence that the drug was effective.

... In one memo to Califf, division director Ellis Unger challenges Woodcock’s scientific judgement and warns that Califf and Woodcock’s decision could set a new precedent for the accelerated approval of rare disease medicines.

Unger also disputes Califf’s conclusion that Woodcock followed proper procedures, arguing instead “there was no scientific basis underlying the conclusion ... this was simply a judgement call by Dr. Woodcock.”

See the documents: [More](#).

Michelle M. Bolek, MPH
Office of Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
O: 301-796-2973
BB: 240-447-4682
michelle.bolek@fda.hhs.gov

From: [Huang, Shiew Mei](#)
To: [Woodcock, Janet](#); [Huang, Shiew Mei](#)
Subject: Kesselheim JAMA paper on eteplirsen
Date: Tuesday, October 25, 2016 11:06:31 PM
Attachments: [Aaron Kesselheim Jerry Avorn JAMA Oct 24 2016 eteplirsen jvp160151.pdf](#)

Janet, as a follow up to our brief conversation after today's Medical Policy meeting on drug interactions, here is the JAMA paper by one of our AC members who voted against the approval of eteplirsen. Shiew-Mei

Shiew-Mei Huang, PhD
Deputy Director
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Office of Translational Sciences
Center for Drug Evaluation and Research
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Program Support Specialist
Karen Graves
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VIEWPOINT

Approving a Problematic Muscular Dystrophy Drug Implications for FDA Policy

Aaron S. Kesselheim, MD, JD, MPH
Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Jerry Avorn, MD
Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

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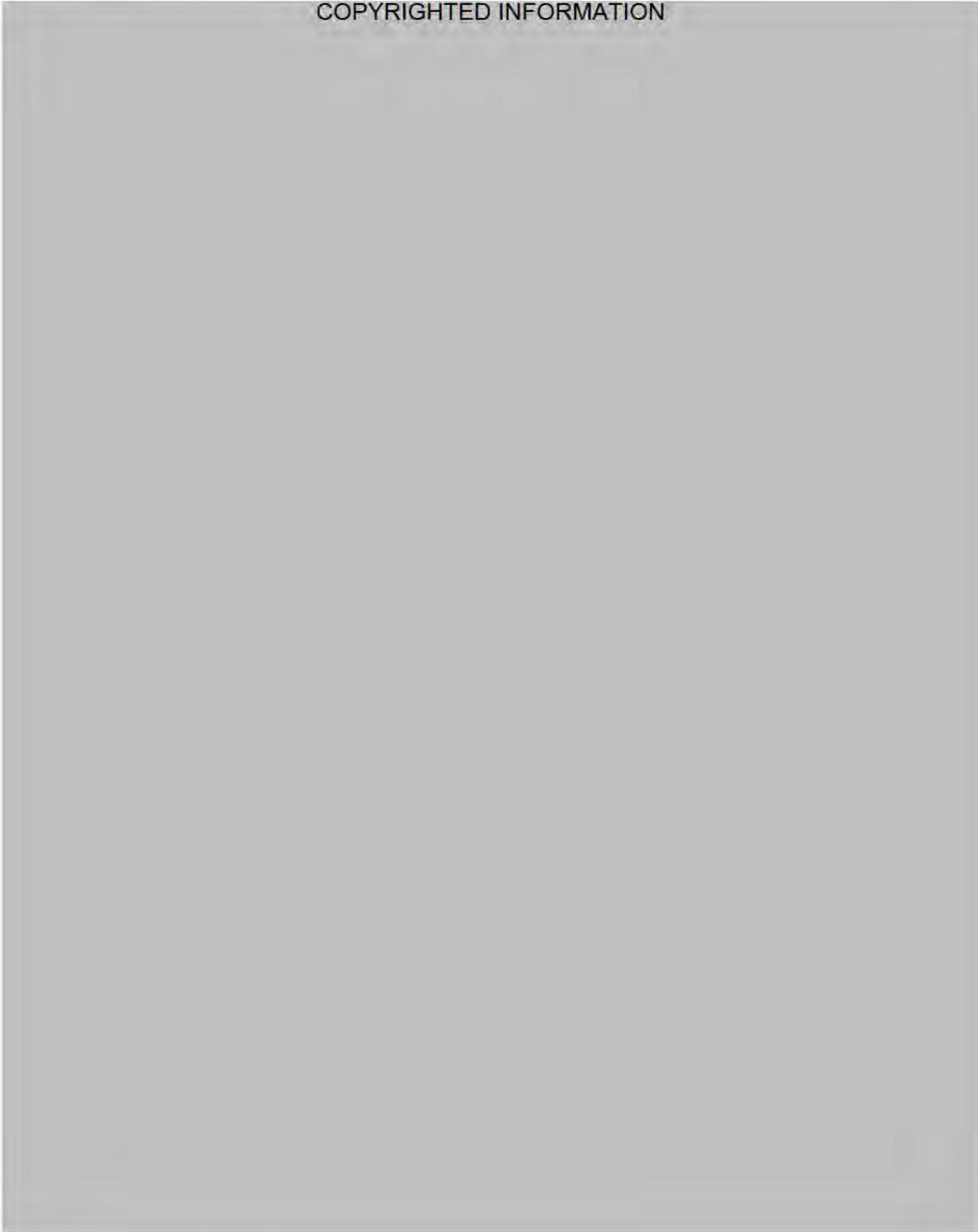
jama.com

JAMA Published online October 24, 2016

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From: [Jenkins, John K](#)
To: [Woodcock, Janet](#)
Cc: [Jenkins, John K](#)
Subject: RE: NORD
Date: Wednesday, October 19, 2016 8:24:33 AM

Christine McSherry was at the meeting yesterday and gave me a lecture during the Q&A about her disappointment with my comments about lessons learned from Sarepta. She also commented about how her son is improving on eteplirsen. I did not engage with her and simply said in response that the drug is approved, that I hoped her son is benefiting, and that Sarepta should enroll and complete the PMR in a timely manner. I'm not sure if she sought you out during the meeting to complain about my comments.

In a private side bar, Shamin Ruff (?sp) from Sarepta told me that she agreed with all my comments. She was quite emotional about her experience through the whole process and said she and Ed Kaye were very disappointed in 2013 when we told them we would consider an NDA based on dystrophin measures. She said they had been waging an intense battle with their CEO at the time to start a new trial and that feedback from FDA undercut any ability they had to press for a new trial. She also expressed disappointment that our PMR did not call for a placebo controlled trial, which she said they could have done in Europe or some other country where the drug is not approved. I noted there are ethical issues in FDA requiring a trial that cannot be done in the US where the main benefit of the outcome of the trial would be to US patients (i.e., full approval here, not in the countries where the study was conducted). She also said she was not sure Sarepta could afford to conduct the dose-response trial called for under the PMR since the cost might be very high given cost of goods for a 7X higher dose. It was an interesting, somewhat surreal conversation.

From: Woodcock, Janet
Sent: Tuesday, October 18, 2016 9:52 AM
To: Jenkins, John K
Subject: RE: NORD

These are very good, can I borrow them. I'm sure I will be asked this a lot. Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: October 18, 2016 at 8:17:30 AM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: RE: NORD

Here are my lessons learned:

- A poorly planned and executed development program for a rare disease misuses valuable patient resources and serves to delay obtaining the knowledge required to understand the benefits and risks of a drug to support regulatory review and approval

- FDA provides valuable advice and guidance to sponsors, we cannot require sponsors to follow our advice
 - Path taken by Sarepta **NOT** a good model for other development programs
- Assays for biomarkers should be well validated before use to avoid obtaining misleading information and wasting clinical specimens
 - Particularly true when invasive procedure required to collect tissue in children
- Rigorous blinding and control procedures should be in place to minimize bias in assay interpretation
 - Protocol should specify blinding procedures, adjudication methods, independence of readers, etc.
- In many cases, randomized controlled clinical trials represent the fastest way to determine if a drug is effective
 - Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials
 - Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)
 - Report early trial results accurately, *post hoc* analyses of failed trials are generally hypothesis generating for next trial, not evidence to support approval
- In many cases, randomized controlled clinical trials represent the fastest way to determine if a drug is effective
 - Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials
 - Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)
 - Report early trial results accurately, *post hoc* analyses of failed trials are generally hypothesis generating for next trial, not evidence to support approval
- Use of accelerated approval pathway should be prospectively planned, **NOT** as a “rescue” for a failed program
 - Sponsor and FDA should agree on the surrogate and drug effect considered “reasonably likely” to predict clinical benefit **before** unblinding data
 - “Any” effect of a drug on a biomarker is not a basis for AA
 - Ideally, the confirmatory trial to further define clinical benefit should be started before AA is granted to ensure the trial will be completed in a timely manner
- FDA welcomes the engagement of patients and caregivers in helping to design development programs that will result in drugs that provide meaningful clinical benefit to those with disease
- Approval decisions must be based on data from adequate and well-controlled clinical trials, which may include PROs and other patient-derived measures
- Experience of patients enrolled in trials can be very helpful; discordant results between trial data and patient anecdotes are very hard to reconcile
- FDA reviewers are committed to facilitating development of effective and safe drugs for rare diseases
- Upholding statutory standards for approval in face of hopes and desires of patients, families, sponsors, and investors is a very difficult job
- Personal attacks on FDA reviewers creates an atmosphere of distrust and isolation rather

than collaboration

- Recruitment and retention of qualified review staff is very challenging in such an environment

Comments welcome.

John

From: Woodcock, Janet
Sent: Tuesday, October 18, 2016 8:13 AM
To: Jenkins, John K
Subject: Re: NORD

For some reason my phone can't open the file. Yesterday when asked this at the biotech meeting I said randomize early, use valid assays, consider adaptive designs, do interim analyses, don't assume a rapid treatment effect. Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: October 18, 2016 at 7:31:49 AM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: NORD

Janet

I am speaking at NORD today in a session Rich is chairing on Regulatory Flexibility. Attached are my slides. I welcome any input you have on the section at the end about lessons learned from eteplirsen and other recent drugs for rare diseases.

John

From: [Rao, Ashutosh](#)
To: [Woodcock, Janet](#)
Subject: RE: any progress on that letter to the neuro journal?
Date: Monday, October 03, 2016 2:33:11 PM
Attachments: [Saper_2_rmc.doc](#)
[Saper_2.doc](#)

Hi Janet,

Suggested edits are attached.

Ellis had previously asked for input and a second file (Saper_2.doc) with two technical edits I have already sent him is also attached.

Best,
Ash

From: Woodcock, Janet
Sent: Monday, October 03, 2016 12:59 PM
To: Rao, Ashutosh
Subject: FW: any progress on that letter to the neuro journal?

Ash, confidentially, can you just take a look at this and make sure it is technically correct? Rob may want to sign on to it. jw

From: Califf, Robert
Sent: Saturday, October 01, 2016 11:29 AM
To: Unger, Ellis
Cc: Woodcock, Janet; Jenkins, John K
Subject: RE: any progress on that letter to the neuro journal?

Ellis,

A few edits. Let me know what you think. Yes, I'd like to be a coauthor, as there are policy implications for our NIH efforts here. I'm interested in Janet and John's views also.

It may be that the best course would be for the journal to publish the letter with a reply from the authors.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Friday, September 30, 2016 3:46 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

Thanks! She's starting to move in the right direction.

Here's a draft letter. Feel free to comment/revise, and I'm more than happy for you to sign it if you wish.

Ellis

From: Califf, Robert
Sent: Friday, September 30, 2016 8:10 AM
To: Unger, Ellis
Subject: RE: any progress on that letter to the neuro journal?

No problem. I'm happy to look at a draft over weekend.
Hope all is well with (b) (6)

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Thursday, September 29, 2016 6:19 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

Sorry – I've been wrestling this week with (b) (6) illness, but will get on it now.

From: Califf, Robert
Sent: Thursday, September 29, 2016 5:44 PM
To: Unger, Ellis
Subject: any progress on that letter to the neuro journal?

Robert M Califf MD
Commissioner of Food and Drugs



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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Editor-in-Chief
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c/o Managing Editor
330 Brookline Avenue
Boston, MA 02215
email: aon@bidmc.harvard.edu

Dear Dr. Saper:

(b) (5)

FDACDER000662

(b) (5)





From: [Unger, Ellis](#)
To: [Woodcock, Janet](#); [Jenkins, John K](#)
Cc: [Califf, Robert](#)
Subject: RE: any progress on that letter to the neuro journal?
Date: Saturday, October 01, 2016 2:18:51 PM

Janet/John,

Here was my response to Rob:

Rob,

Your edits are fine with me.

With respect to your query (did they really give the impression that a “positive” fiber is a “normal” fiber?), I believe they did. First of all, the word “positive” strongly implies a binary variable. They never provide any information that suggests that a “positive” fiber is anything other than fully normal. Shame on them. (I’ll add that the 50% positive figure misled a number of people in CDER, giving them the false impression that eteplirsen had a robust treatment effect.) Second, readers are likely to infer that a “positive” fiber is essentially normal because they claim that: “Eteplirsen restored dystrophin in the 30 and 50 mg/kg/wk cohorts...” based on ~ 50% positive fibers. Third, their bioquant assay measures staining intensity. Responsible investigators would have used those results to explain how very meager the signal was, but these authors never bothered to interpret the bioquant findings for the reader (or FDA).

Another point that could be made is that the Western blot findings from Study 301 (median dystrophin increase = 0.1%) disproves the astounding results of the paper.

Ellis

From: Califf, Robert
Sent: Saturday, October 01, 2016 11:29 AM
To: Unger, Ellis
Cc: Woodcock, Janet; Jenkins, John K
Subject: RE: any progress on that letter to the neuro journal?

Ellis,

A few edits. Let me know what you think. Yes, I’d like to be a coauthor, as there are policy implications for our NIH efforts here. I’m interested in Janet and John’s views also.

It may be that the best course would be for the journal to publish the letter with a reply from the authors.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Friday, September 30, 2016 3:46 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

Thanks! She's starting to move in the right direction.

Here's a draft letter. Feel free to comment/revise, and I'm more than happy for you to sign it if you wish.

Ellis

From: Califf, Robert
Sent: Friday, September 30, 2016 8:10 AM
To: Unger, Ellis
Subject: RE: any progress on that letter to the neuro journal?

No problem. I'm happy to look at a draft over weekend.
Hope all is well with (b) (6).

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Thursday, September 29, 2016 6:19 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

Sorry – I've been wrestling this week with (b) (6) illness, but will get on it now.

From: Califf, Robert
Sent: Thursday, September 29, 2016 5:44 PM
To: Unger, Ellis
Subject: any progress on that letter to the neuro journal?

Robert M Califf MD
Commissioner of Food and Drugs

From: [Murphy, Dianne - OC](#)
To: [Woodcock, Janet](#)
Subject: Re: right decision
Date: Monday, September 26, 2016 7:54:12 PM

You are so correct! No one talks it about anymore.....

Our FDA immunologists were saying CD4 counts were not reliable and discounted some of the industry efforts in this area. Carl Peck pulled in people from the U. Of Maryland and Jim Bilstead worked with Carl on meeting with NIH on CD4's and other possible surrogates and even Kessler worked in supporting these efforts. Carl, Jim and I had to ask NIH to request a DSMB at NIH to break their blind- they said we had to speak with the DSMB, which we did and they broke the blind and gave us the data. I remember reviewing it in my kitchen!!

It was an average difference of something like 11- 14 CD4 cell difference between arms and we approved it! DDI if I recall all of this from memory - a little foggy.

Yes, internal staff were at first NOT budging and it took the "big guys" to step in and help make it happen.

Leadership is so critical to any organization and I cannot say enough good things about your willingness to take a stand when you are going against "the grain" at FDA (eg Thalidomide) , but it is both clinically and scientifically the right thing to do.

FDA ossifies if someone does not prevent it.

Apologies for length.

Dianne

Sent from my BlackBerry 10 smartphone.

From: Woodcock, Janet
Sent: Monday, September 26, 2016 2:03 PM
To: Murphy, Dianne - OC
Subject: RE: right decision

Thanks much for reading all the material, and your continuing support! As you know, the "status quo" is pretty upset about this one, but I recall that was the case with the early HIV drugs as well.
jw

From: Murphy, Dianne - OC
Sent: Friday, September 23, 2016 7:12 PM
To: Woodcock, Janet
Subject: right decision

Janet,

In my humble opinion, you are absolutely correct in the opinion and approach you took.

I have not been deeply involved in the present discussion of the approval of eteplirsen but read your review and the summary of others.

Having previously been deeply involved with the HIV crises, I think there are many similarities. It

took people with an open attitude, a deep understanding of the underlying disease process while knowing there was still much to learn, courage to made decisions when we knew we did not know all we wished we could know and a willingness to shake up the status quo, as it just did not work for the issues at hand. You just demonstrated all of those attributes.

Congratulations on your decision.

Dianne

Dianne Murphy, MD, FAAP
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA

Dianne.Murphy@fda.hhs.gov
301-796-8651
Website: <http://www.fda.gov/pediatrics>

From: [Temple, Robert](#)
To: [Unger, Ellis](#); [Jenkins, John K](#); [Dunn, Billy](#); [Bastings, Eric](#); [Woodcock, Janet](#)
Subject: FW: Manuscript for review: Exondys 51 for DMD
Date: Thursday, September 22, 2016 1:41:48 PM
Attachments: [Exondys 51 for DMD Circdraft.doc](#)

From: The Medical Letter [<mailto:editor@medicalletter.org>]
Sent: Thursday, September 22, 2016 1:35 PM
To: Temple, Robert
Subject: FW: Manuscript for review: Exondys 51 for DMD

Attached is a circulating draft from Jean-Marie Pflomm, Pharm.D.

May we have your comments by September 29th

The Medical Letter®

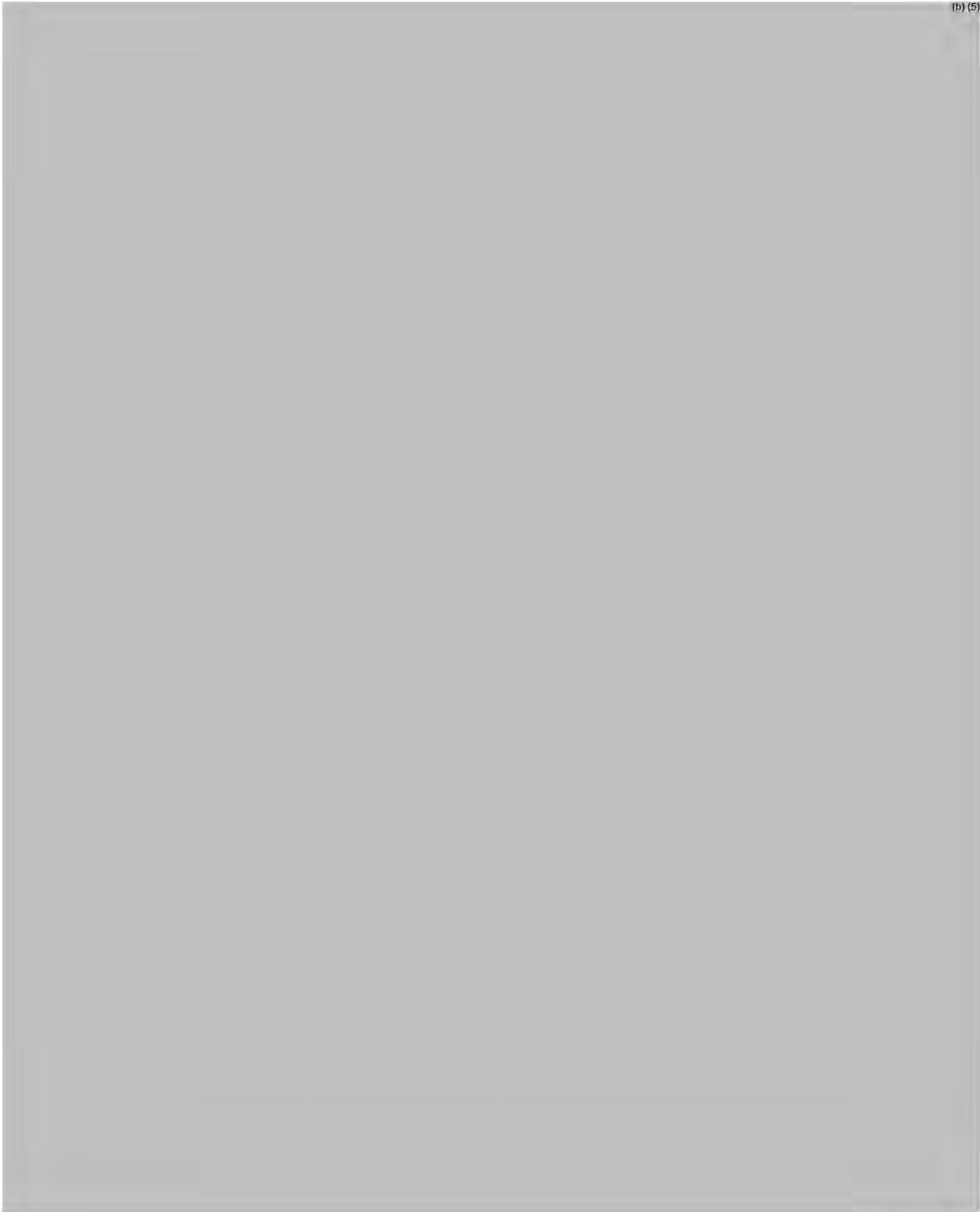
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www.medicalletter.org
e-mail: editor@medicalletter.org

This is a preliminary draft of an article prepared for *The Medical Letter*.

We welcome your comments or corrections. Due Date: September 29, 2016

(b) (5)





From: [Jenkins, John K](#)
To: [Frank J. Sasinowski](#); [Unger, Ellis](#); [Woodcock, Janet](#)
Cc: [Jenkins, John K](#)
Subject: RE: eteplirsen and "reasonably likely to predict"
Date: Wednesday, September 21, 2016 4:04:56 PM

Frank

If you want to submit your analysis in writing, we will be happy to take a look.

John

From: Frank J. Sasinowski [<mailto:FSasinowski@hpm.com>]
Sent: Wednesday, September 21, 2016 3:36 PM
To: Unger, Ellis; Woodcock, Janet; Jenkins, John K
Cc: Frank J. Sasinowski
Subject: RE: eteplirsen and "reasonably likely to predict"

totally understand!
thanks for letting me know.
onward.
frank

From: Unger, Ellis [<mailto:Ellis.Unger@fda.hhs.gov>]
Sent: Wednesday, September 21, 2016 1:03 PM
To: Frank J. Sasinowski; Woodcock, Janet
Cc: Jenkins, John K
Subject: RE: eteplirsen and "reasonably likely to predict"

Dear Frank,

I know you are well-meaning, and I deeply respect your extensive knowledge and experience in the rare disease/accelerated approval space. At this point, however, I'm not planning to discuss the eteplirsen NDA with anyone outside the Agency.

Best,

Ellis

From: Frank J. Sasinowski [<mailto:FSasinowski@hpm.com>]
Sent: Tuesday, September 20, 2016 9:41 AM
To: Woodcock, Janet; Unger, Ellis
Cc: Frank J. Sasinowski
Subject: eteplirsen and "reasonably likely to predict"

greetings, drs. woodcock and unger,
I write to you this morning not as counsel to sarepta, but as one

versed in the statutory requirements and FDA precedents on quantum of evidence of effectiveness.

I write because I deeply care about the public understanding of the basis of FDA's actions.

last night I read all the documents that FDA released on yesterday's action.

you both concur that there was at least one adequate and well controlled study that established dystrophin production.

the key issue on which your opinions differ is whether that level of dystrophin qualifies as "reasonably likely to predict clinical benefit".

my view of the clinical evidence is a bit different from each of yours and this view stems from FDA precedents, both of accelerated approvals and of rare disease therapies.

I may be wrong but I think that my view may reconcile your disparate positions on "reasonably likely to predict".

I am available anytime today or tomorrow to come by to meet with either or both of you to share this.

(alternatively, I can try to outline it in an email but that loses ability for your interrogation of this perspective and important colloquy.)

on Thursday and Friday I am on the road in dallas (with drug company) and cincinnati (keynoter at medical conference on rare lung diseases).

next week I will be at white oak on weds, on thu and on fri for cder meetings and could easily swing by after any one of those meetings.

(those meetings end at 5 on weds., at 2 on thur and at noon on fri. and meeting at one of those times would be convenient as I would be at your office complex.)

why do I care?

you each express potential consequences or understandings of this

action, some of which would not advance new therapies for rare diseases.

you each have invested your extensive professional expertise as well as a personal commitment to your review of this therapy. my view of the quantum of evidence and precedents may “square” your respective views on “reasonably likely to predict”, and a unified view on this action from senior FDA officials would likely be welcome by all.

eager to try to reconcile the available evidence with the regulatory standards in a way that does not disagree with any element in either of your respective positions as can be discerned from last night’s reading of the available documents.

onward.

frank

Frank J. Sasinowski

Kindly consider reviewing my analyses of FDA orphan drug approvals and Subpart H approvals:

Frank Sasinowski & Alexander Varond, FDA’s Flexibility in Subpart H Approvals: Assessing Quantum of Effectiveness Evidence, 71 Food and Drug L.J. 135 (2016), Also, see FDA Law Blog.

Frank Sasinowski, James Valentine et al., Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014, Therapeutic Innovation & Regulatory Sci. 1 (2015).

Frank Sasinowski, Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs, 46(2) Drug Info. J. 238 (2011).

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From: Unger, Ellis
To: LaVange, Lisa
Cc: Borio, Luciana; Califf, Robert; Woodcock, Janet; Jenkins, John K
Subject: RE: OB concurrence
Date: Tuesday, September 20, 2016 3:38:37 PM
Attachments: Stats review.pdf

Lisa,

I regret that I referred to the "Office of Biostatistics" as the "Office of Biometrics" in my CR memorandum and appeal to the Agency Scientific Dispute Process Board. I hadn't noticed my error when I wrote and filed these documents. (I believe there was an "Office of Biometrics" in the past.)

The review from the Office of Biostatistics (from Xiang Ling, Kun Jin, and Jim Hung, 5/3/16) concluded: "The data, overall, did not provide statistical evidence to support the efficacy of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping." Their review (attached), focused on Studies 201 and 202, never considered the issue of accelerated approval.

I wrote in my CR memo; "I agree with the views of ... the Office of Biometrics ... that the applicant has not provided substantial evidence of effectiveness from adequate and well controlled trials to support conventional approval." Based on the Ling/Jin/Hung review, I believe my statement is true.

I wrote in my appeal memo "NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a complete response action. This view was shared by the Office of Biometrics, which performed the statistical review...." I believe this statement is also true.

With respect to the interim results of Study 301, the study that ultimately became the basis for accelerated approval, I now recognize that a statistical review was never filed in DARRTS. Fanny Choy, the project manager for the NDA, sent an email Drs. Jin, Ling, and Hung announcing that an amendment had arrived with the interim data from Study 301, but I find no review in the record.

Having now drawn my attention to these facts, I would say there was neither concurrence nor disagreement from the Office of Biostatistics with respect to the decision to grant accelerated approval for eteplirsen. Once Dr. Woodcock filed her memo on 7/14/16, I felt extraordinary pressure to complete my own memo as rapidly as I could. Had there been a biostatistics review of Study 301 in DARRTS, I certainly would have cited their views.

Ellis

From: LaVange, Lisa
Sent: Tuesday, September 20, 2016 10:59 AM
To: Unger, Ellis; Jenkins, John K
Cc: LaVange, Lisa
Subject: OB concurrence

I just saw this in the Pink Sheet and am guessing the reference to the Office of Biometrics (which does not exist) came from Ellis' dispute letter citing that the Office of Biometrics concurred with the CR decision. As far as I know, there has been no concurrence with opposition to the accelerated approval decision at the team, division, or office level within the Office of Biostatistics. If you think you have concurrence, I would be interested to hear what that is based on.

This also highlights a problem with how OND views concurrence, or at least ODE I. The team, and possibly the Division of Biometrics I, concurred with the CR. The Office of Biostatistics did not concur, because we were not asked (by ODE I or OND). Normally, I am only asked to weigh in on individual drug decisions when they are disputed at the OND director level. Occasionally, a medical division will ask for OB input, but that is rare. So, Ellis' letter was incorrect, and I pointed that out to Janet and Rob, when asked. Regarding concurrence with the accelerated approval decision, OB's position was that the permutation t-test showed a statistically significant change between pre-and post- dystrophin levels. The test used was appropriate, and the p-value interpretable. The clinical meaningfulness of the change was not a topic we weighed in on, at least not to my knowledge. If you have different understanding, let me know.

Lisa

FDA Staff Opposed To Accelerated Approval

- Office of Drug Evaluation | Director Ellis Unger
- Division of Neurology Products review team

Office of Biometrics

- Office of Clinical Pharmacology
- Office of New Drugs Director John Jenkins
- Acting Chief Scientist Luciana Borio

Unger's appeal was heard by the agency's Scientific Dispute Process Review Board, a standing committee chaired by acting Chief Scientist Luciana Borio. The board reviewed the eteplirsen NDA administrative file and interviewed Unger, Woodcock, an unidentified review team member and CDER Ombudsman Virginia Behr.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/BLA #: 206488
Drug Name: EXONDYS 51™ (eteplirsen)
Indication(s): Duchenne muscular dystrophy (DMD)
Applicant: Sarepta
Date(s): Submission date: 6/26/2015
PDUFA Date: 2/26/2016
Review Priority: Priority Review

Biometrics Division: Division I, Office of Biometrics (HFD -710)
Statistical Reviewer: Xiang Ling, Ph.D.
Concurring Reviewers: Kun Jin, Ph.D., Team Leader
Jim Hung, Ph.D., Director

Medical Division: Division of Neuropharm (HFD -120)
Clinical Team: Christopher Breder, M.D., Ph.D.
Ronald Farkas, M.D., Ph.D., Team Leader
Project Manager: Fannie Choy

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1 EXECUTIVE SUMMARY

The data, overall, did not provide statistical evidence to support the efficacy of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The only randomized controlled study submitted by the applicant, Study 201, can only be considered as exploratory because of study design and statistical analysis issues. In Study 201, patients were randomized to receive 50 or 30 mg/kg eteplirsen, or placebo. The study endpoints were assessed through Week 24. The statistical analysis plan of Study 201 did not include a method for statistical adjustment for testing multiple doses and/or multiple endpoints. The primary endpoint in Study 201 was the percent of dystrophin positive fibers in muscle biopsy tissue. The interpretation of the immunohistochemistry raw data is discussed in the clinical review. There was no nominally significant difference between eteplirsen 50 mg/kg, eteplirsen 30mg/kg and placebo for the 6MWT, which was the key clinical endpoint in Study 201.

The comparison of eteplirsen with historical controls, as proposed by the applicant in the open-label extension of Study 201 (called Study 202 by the applicant), is statistically uninterpretable, as this open-label extension did not have a prespecified statistical analysis plan, and had an inadequate control for bias. Among the potential sources of bias in the open-label extension of Study 201 are possible differences in various factors between eteplirsen-treated patients and the selected historical control cohort unaddressed by the applicant's attempt to match patients, the potential selection bias due to the *post-hoc* identification of the control cohort by the applicant, and other known sources of bias with the use of a historical control.

2 INTRODUCTION

2.1 Overview

Study 201 is the only randomized, double-blind, placebo-controlled study in this application. It was conducted at a single site in US in 12 subjects with genotypically confirmed DMD. Efficacy was assessed through the first 24 weeks of this study, while safety was assessed through Week 28. Upon completion of Study 201, all 12 patients were enrolled into an open-label extension study (Study 202) to continue receiving once-weekly treatment with eteplirsen. Study 202 was still ongoing at the time of NDA submission and interim study results were submitted for a cumulative 168 weeks of treatment, from Week 1 in Study 201 through the interim data cut at Week 140 in Study 202.

A historical control cohort was identified from 2 DMD patient registries for comparison to eteplirsen-treated patients in Study 201/202.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\NDA206488\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dmd-51 and \\CDSESUB1\evsprod\NDA206488\0006\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The key clinical efficacy endpoint results were reproduced by this reviewer from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The first patient was enrolled in Study 201 on July 18, 2011 and the study was completed on February 29, 2012. Protocol 201 was amended 7 times, 3 of them were implemented after the study was initiated and the last version was dated January 07, 2012. In Amendment 6 (dated November 04, 2011), the protocol changed the endpoint of 6-Minute Walk Test (6MWT) from exploratory endpoint to a secondary endpoint. In Amendment 7 (dated January 07, 2012), the duration of the study was extended from 24 to 28 weeks. The efficacy analyses were only specified in the statistical analysis plan (SAP), dated February 20, 2012.

Study 201 was not designed as a clinical efficacy study and not powered for efficacy analysis. The primary endpoint was the percent of dystrophin positive fibers as measured in muscle biopsy tissue, i.e., a biomarker. The key clinical secondary endpoint, 6MWT, was specified midway through the trial and the analyses were not specified until the trial was close to completion.

Study Design

This is a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly i.v. infusions of eteplirsen in subjects with genotypically confirmed DMD with an appropriate genetic lesion. Eligible subjects were randomized to receive 50 or 30 mg/kg eteplirsen or placebo, then placebo subjects were further randomized to 1 of 2 groups to create 4 treatment groups as shown in Table 1. Groups 1 and 2 received 50 or 30 mg/kg eteplirsen once a week for 28 weeks. Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks, and Group 3b received

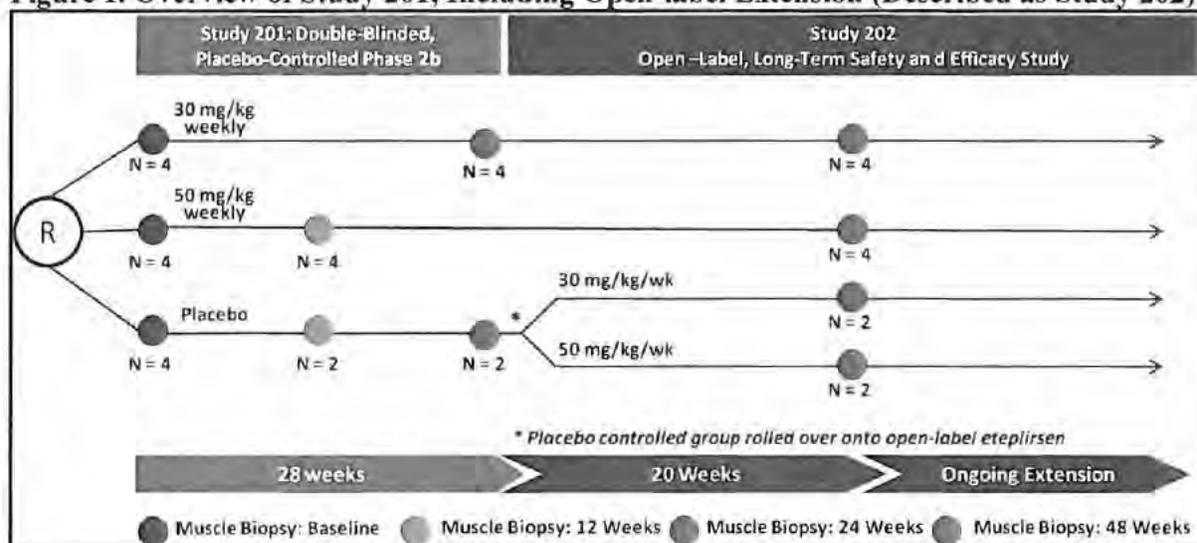
placebo once a week for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks. Beginning Week 25, all parties were aware that all subjects were receiving either 50 or 30 mg/kg eteplirsen.

Table 1: Treatment Groups

Group	N	Treatment
1	4	50 mg/kg eteplirsen IV once weekly for 28 weeks
2	4	30 mg/kg eteplirsen IV once weekly for 28 weeks
3a	2	Placebo IV for 24 weeks then 50 mg/kg eteplirsen for 4 weeks
3b	2	Placebo IV for 24 weeks then 30 mg/kg eteplirsen for 4 weeks

All patients underwent muscle biopsies at baseline for analysis of exon skipping and dystrophin expression. Repeat biopsies were performed at Week 12 for patients in Group 1 and Group 3a and at Week 24 for patients in Group 2 and Group 3b. Efficacy was assessed through the first 24 placebo-controlled weeks of this study, while safety was assessed through Week 28. Upon completion of this study, all 12 patients were rolled into an open-label extension (called Study 202 by the applicant) to continue receiving once-weekly treatment with eteplirsen for additional 212 weeks. In the open-label extension, all patients underwent a third muscle biopsy from the deltoid muscle at Week 20 and optionally a fourth muscle biopsy at approximately Week 140.

Figure 1. Overview of Study 201, Including Open-label Extension (Described as Study 202)



Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from baseline in percent of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry (IHC) at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.

Key Efficacy Endpoints:

1. Changes from Baseline in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.
2. Changes from Baseline to Week 24 in 6-Minute Walk Test (6MWT).

The following clinical assessments were described as exploratory endpoints in the protocol (Amendment 7, dated 07 January 2012), but are included as key secondary endpoints together with 6MWT in the SAP (dated February 20, 2012):

- Timed 4 Step Test.
- Maximum voluntary isometric contraction test (MVICT) to measure elbow flexion and extension, knee flexion and extension, and grip strength.
- Timed 10-meter run from the North Star Ambulatory Assessment (NSAA).
- NSAA total score.

There is no clear description of hierarchal ordering among all those secondary endpoints. In the open-label extension (described as Study 202) only 6MWT is included as primary clinical endpoint.

3.2.2 Statistical Methodologies

Testing and summary statistics of all efficacy endpoints will combine placebo subjects into a single group. Some efficacy assessments including 6MWT were performed on Days 1 and 2 of the Week 1 (baseline), Week 12, and Week 24 visits and once at the Week 4, 8, 16, and 20 visits. On those visits where 2 tests were performed, the maximum/best observed value is used for the primary analysis. If data for any one visit day are missing, then the non-missing value from the same visit is used.

Efficacy Analysis Population

The efficacy analysis set is the Full Analysis Set (FAS), consisting of all subjects randomized into the study who received any amount of study drug.

Statistical Analysis Method

For this exploratory study, all statistical analyses are conducted at two-sided alpha level of 0.05. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints, so all p-values are exploratory only.

The primary efficacy endpoint, the change from baseline in percent of dystrophin positive fibers, was analyzed by comparing the 50 mg/kg eteplirsen treatment group at Week 12 to the combined placebo treatment group, and the 30 mg/kg eteplirsen treatment group at Week 24 to the combined placebo treatment group, using the ANCOVA for ranked data with Baseline values and duration of DMD as covariates.

The analysis of changes from baseline to Week 24 in the clinical assessment parameters (6MWT, Timed 4 Step Test, MVICT, Timed 10-meter run, and NSAA total score) was based on a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with treatment (placebo, 30 mg/kg, 50 mg/kg), time, and treatment-by-time interaction terms as fixed effects, subject nested within treatment as random effects, with the Baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix is used. The treatment comparison is made between each of the active treatments and placebo. The same MMRM analysis described above would be repeated to compare the combined eteplirsen groups to placebo.

If there was strong evidence suggesting that data for any endpoint deviated from normal distribution, then ANCOVA for ranked data was to be utilized.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were recruited for this study nationwide across the US. A total of 12 patients were randomized and all patients received scheduled infusions of study medication and completed the study as planned. All patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white. The time since DMD diagnosis ranged from 18 to 112 months, with a median duration of 57 months. Numerically, there appears to be some imbalance in baseline 6MWT among the treatment groups (Table 2).

Table 2: Demographic and Baseline Disease Characteristics

Parameter		Placebo to Eteplirsena N = 4	Eteplirsen			All Patients N = 12
			30 mg/kg N = 4	50 mg/kg N = 4	All Eteplirsen N = 8	
Age	Mean	8.5	9.3	8.5	8.9	8.8
	Median	8.5	9	8.5	9	9
	Min, Max	7, 10	9, 10	7, 10	7, 10	7, 10
Mutation, n (%)	45-50	0	2 (50.0)	1 (25.0)	3 (37.5)	3 (25.0)
	48-50	0	1 (25.0)	0	1 (12.5)	1 (8.3)
	49-50	3 (75.0)	0	2 (50.0)	2 (25.0)	5 (41.7)
	50	1 (25.0)	0	0	0	1 (8.3)
	52	0	1 (25.0)	1 (25.0)	2 (25.0)	2 (16.7)
6MWT, meters	Mean	394.5	355.3	396	375.6	381.9
	Median	379	359	395	380.5	380
	SD	42.25	74.78	26.61	56.34	50.92
	Min, Max	364, 456	261, 442	365, 429	261, 442	261, 456
Time since DMD diagnosis, months	Mean	50.3	52.5	66.5	59.5	56.4
	Median	51	57	68	57	57
	SD	13.74	14.06	44.29	31.33	26.4
	Min, Max	36, 63	32, 64	18, 112	18, 112	18, 112

^a Includes both 30 mg/kg and 50 mg/kg

Source: Table 10-2 and 10-3 of the CSR.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

The following analyses were based the fiber data derived by the applicant. The validity of the immunohistochemistry (IHC) raw data is beyond the scope of this review, and is addressed in the clinical review, to which the reader is referred for interpretation of the IHC results.

There was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p = 0.958$; Table 3). At Week 24, the mean percentage of dystrophin-positive muscle fibers was higher in the eteplirsen 30 mg/kg group than the placebo. Patients treated with 30 mg/kg eteplirsen demonstrated 23% increase in the mean percentage of dystrophin positive fibers from baseline to Week 24. There appeared to be no increases from baseline in placebo patients. The nominal p value (0.002) for the comparison between eteplirsen 30 mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type I error due to multiple comparisons, and the other comparison between 50mg/kg and placebo in Study 201 was negative.

Table 3: Dystrophin-Positive Fibers Detected by IHC with MANDYS106

Time point		Placebo	30 mg/kg Eteplirsen N = 4	50 mg/kg Eteplirsen N = 4
Baseline	Mean	15.64	18.19	11.00
	Median	15.58	17.80	11.51
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment	Mean	11.59	41.14	11.79
	Median	9.44	38.77	11.81
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95	0.79
	Median	-6.13	23.46	2.52
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4
	p-value ^a		0.002	0.958

Source: CSR Table 11-1 and Table 14.2.1.1.2, confirmed by FDA reviewer.

^aBased on ANCOVA model for ranked data with treatment (placebo, 30 mg/kg, 50 mg/kg) as a fixed effect and baseline value and time since DMD diagnosis as covariates.

3.2.4.2 Analyses of 6MWT

As shown in Table 4, placebo-treated patients experienced a mean decline of 17.3 meters in 6MWT from baseline to Week 24, while patients in the 30 and 50 mg/kg eteplirsen groups showed mean declines of 134.8 and 2.3 meters, respectively. ANCOVA for ranked data showed no nominally significant differences between the treatment groups. The result of the MMRM analysis showed a nominally statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo (p=0.026; Table 4).

Table 4: Analysis Results of Change from Baseline in 6MWT

	Placebo	30mg/kg Eteplirsen N = 4	30mg/kg Eteplirsen mITT N = 2	50mg/kg Eteplirsen N = 4
Baseline				
Mean	394.5	355.3	407	396
Median	379	359	407	395
SD(SE)	42.25(21.12)	74.78(37.39)	49.50(35.00)	26.61(13.30)
Min, Max	364, 456	261, 442	372, 442	365, 429
Week 24				
Mean	377.3	220.5	394.5	393.8
Median	377.5	204	394.5	403.5
SD (SE)	19.00 (9.50)	203.14 (101.57)	51.62 (36.50)	53.67 (26.84)
Min, Max	354, 400	43, 431	358, 431	325, 443
Change at Week 24				
Mean	-17.3	-134.8	-12.5	-2.3
Median	-12	-116	-12.5	1.5
SD (SE)	28.06 (14.03)	144.71 (72.36)	2.12 (1.50)	29.89 (14.95)
Min, Max	-56, 11	-296, -11	-14, -11	-40, 28
treatment effect*		-102.4		25.6
95% CI *		(-192.2, -12.5)		(-62.7, 113.8)
P-value *		0.026		0.563

*Based on mixed model repeated measures (MMRM).

Source: Table 14.2.5.2.1 and Table 14.2.5.2.2 of Study 201 CSR,

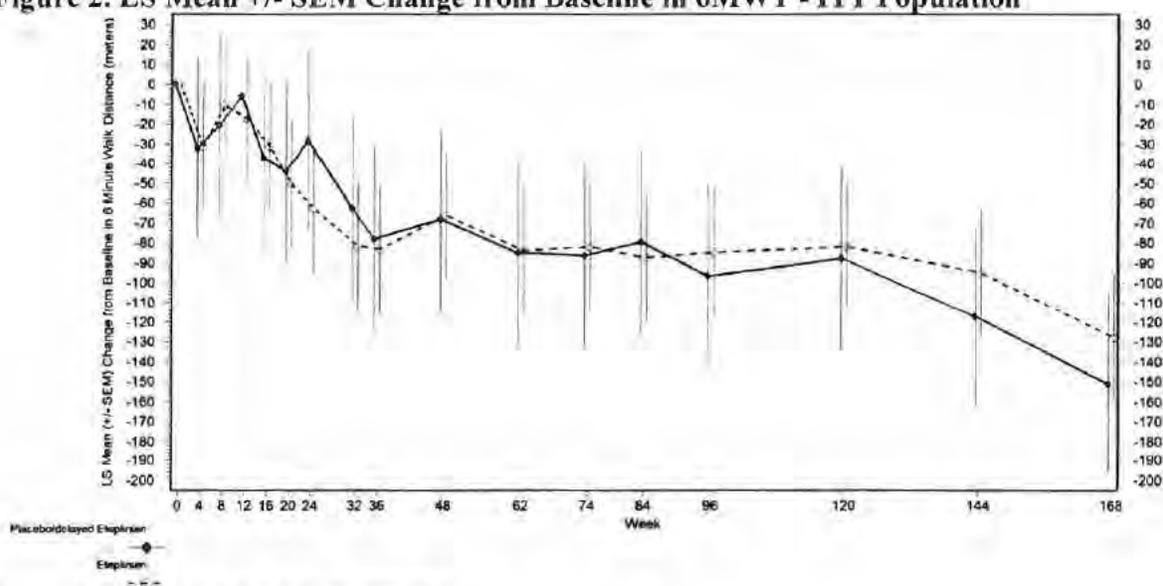
The applicant stated that the large decline in the 30 mg/kg eteplirsen group was attributable to Patients 009 and 010, who showed signs of rapid disease progression within weeks after enrollment. Therefore, the applicant conducted *post-hoc* analyses using Modified Intent-to-Treat (mITT) Population which excluded those 2 patients. For the mITT population, the mean change from baseline to Week 24 in MWT was a decline of 12.5 meters for the 30 mg/kg eteplirsen group. Both ANCOVA on ranked data and the MMRM analysis showed no nominally significant differences between the treatment groups in mITT.

The mITT population was not pre-specified in the SAP. Moreover, the mITT was defined based on the outcome data (instead of enrollment criteria or baseline character). Therefore, analysis on the mITT population could be misleading.

3.2.4.3 Analyses of the open-label extension study (described by the applicant as Study 202)

The 6MWT at Week 168 was compared between the combined eteplirsen group and placebo/delayed eteplirsen group. Analyses on ITT population did not achieve nominal statistical significance ($p=0.68$ by MMRM). The changes from baseline in 6MWT by assessment week for the combined eteplirsen group and placebo/delayed eteplirsen group are shown in Figure 2.

Figure 2. LS Mean +/- SEM Change from Baseline in 6MWT - ITT Population



Source: Figure 14.2.5.2.2.1 of Study 202 CSR.

3.2.4.4 Comparison against Historical Controls

Historical Control Cohort

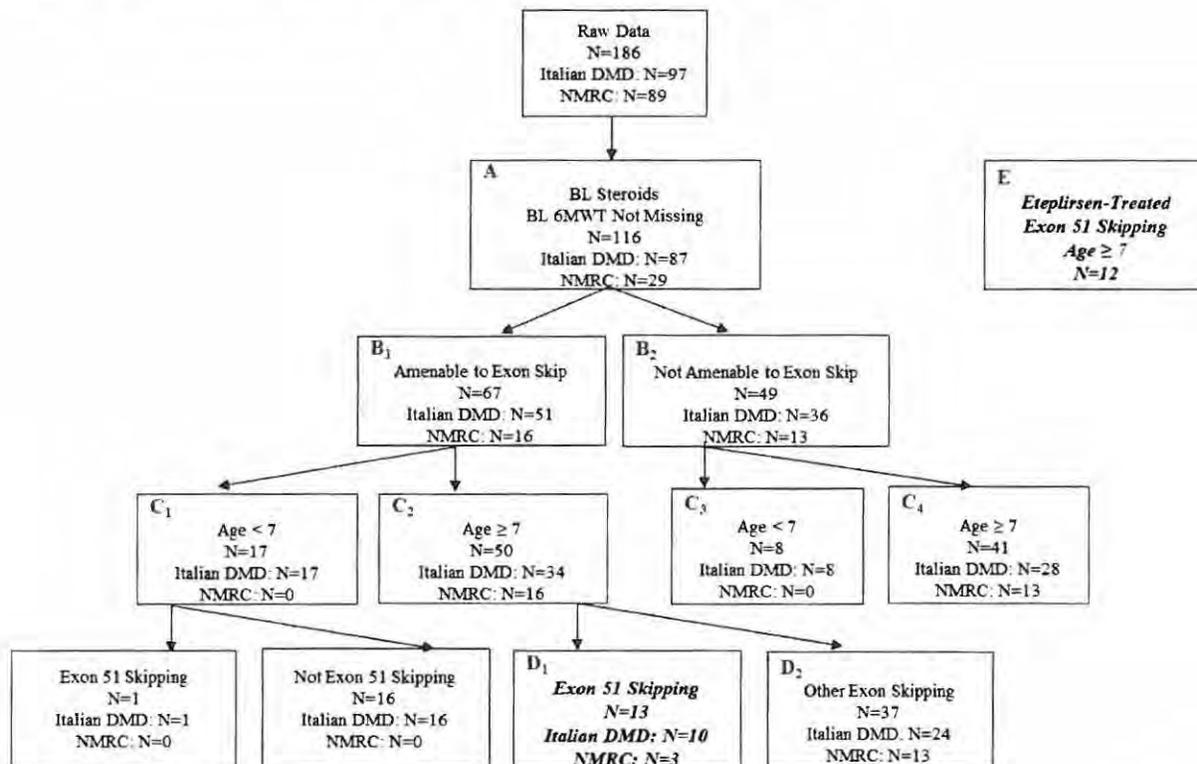
The comparison of eteplirsen with historical controls was not part of an adequate and well-controlled study. The applicant obtained historical data after observations were made for the eteplirsen patients. Historical data were obtained from 2 DMD patient registries (Italian DMD Registry and the Leuven Neuromuscular Reference Center – NMRC) for comparison to eteplirsen-treated patients. The following filters were applied to try to match patients in the historical control cohort:

1. Corticosteroid use at Baseline (use/non-use)
2. Sufficient longitudinal data for 6MWT available
3. Age ≥ 7 years
4. Genotype amenable to any exon skipping therapy
5. Genotype amenable to exon 51 skipping therapy

The Italian DMD registry is a longitudinal multicenter observational cohort study involving 11 tertiary neuromuscular centers in Italy. Patients were recruited between January 2008 and June 2010 and were to be followed for at least three years. The Italian DMD cohort contained the 6MWT results at Baseline (Month 0) and at Months 12, 24, and 36, with age and steroid use entered for each visit and with genotype information for 97 patients. Of these patients, 10 valid cases were identified based on applying the 5 filters.

The NMRC registry was an observational, single center, cohort study of DMD up to 17.5 years of age attending the NMRC between January 2007 and September 2012. The NMRC dataset contained 6MWT results at various time points, the patient's age and steroid use at the same time points, and genotype information for 89 patients. However, discrete visit designations (i.e., Baseline, Month 12, etc.) were not identified in the dataset. The first time points with non-zero meters on the 6MWT assessment for patients who were ≥ 7 years of age and on a steroid, were designated as the Baseline visit. Only 3 cases were identified based on applying filters (Figure 3).

Figure 3: Historical Controls and Eteplirsen-Treated Cohort



Source: Figure 1 of Study SR-15-031 CS.

Applicant's Comparison of Eteplirsen with Historical Control

The results for 6MWT in eteplirsen-treated patients compared with historical controls matched on all 5 criteria mentioned above are shown in Table 5. The difference in LS mean change from baseline on 6MWT at 36 months was 141 meters. The nominal p-value reported by the applicant is not meaningful because the open label extension with historical control comparison was not an adequate and well-controlled study, for the reasons described below.

Table 5: Applicant's Result of 6MWT in Eteplirsen Compared to Historical Controls

Patients Included	Groups Compared		Age	6MWT Baseline	6MWT Month 36**
HC + eteplirsen-treated, Steroid-Treated, Amenable to Exon 51 Skipping, ≥7 years old	HC	N	13	13	11
		Mean / LS Mean ^a (SE)	9.45 (0.403)	357.6 (18.51)	115.1 (33.54)
		Min, Max	7.3, 11.8	200, 458	
	eteplirsen-treated	N	12	12	12
		Mean / LS Mean ^a (SE)	9.41 (0.342)	363.2 (12.18)	256.4 (33.11)
		Min, Max	7.3, 11.0	256, 416	

* LS Mean for 6MWT Month 36 only

** LS Mean difference =141 and p=0.009 at month 36.

Source: Applicant's analyses with output table modified by the reviewer.

Reviewer's Discussion and Conclusion of the Historical Control Study

According to the ICH E10 guidance on Control Group and Related Issues in Clinical Trials, the major and well-recognized limitation of externally controlled (including historical control) trials is inability to control bias. The test group and control group can be dissimilar with respect to a wide range of observable and unobservable factors that could affect outcome. It may be possible to match the historical control group to the test group in observed factors but there is no assurance for any unobserved factors. "The lack of randomization and blinding, and the resultant problems with lack of assurance of comparability of test group and control group, make the possibility of substantial bias inherent in this design and impossible to quantitate."

Because of the serious concern about the inability to control bias, the use of the external control design is restricted only to unusual circumstances.

1. ICH E10 states that "an externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable..." However, such prior belief does not exist for eteplirsen.
2. ICH E10 states that "use of external controls should be limited to cases in which the endpoints are objective..." However, performance on the 6-minute walk test can be

influenced by motivation. Patients may not achieve maximal 6MWT due to concerns of falling or injury, or patients could try harder with encouragement and with the expectation that the drug might be effective.

3. Pocock's criteria¹ for acceptability of a historical control group require that "the methods of treatment evaluation must be the same," and "the previous study must have been performed in the same organization with largely the same clinical investigators." This is especially important when assessing endpoints such as 6MWT, in contrast to hard endpoints such as mortality. For this NDA, these requirements are not met.

Moreover, the historical control group was identified *post-hoc* in this NDA, leading to potential selection bias that cannot be quantitated. If a historical control is to be utilized, selection of the control group and matching on selection criteria should be prospectively planned without knowing the outcome of the drug group and control group.

Based on ICH E10, "a consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." The success criteria for this historical control study were not discussed or pre-specified in the protocol.

Given all these concerns, including issues of comparability of eteplirsen-treated patients and historical control cohort patients, the fact that 6MWT is not a "hard" efficacy endpoint, the potential of selection bias due to the *post-hoc* identification of the control cohort by the applicant, and all the known pitfalls with the use of historical controls, the comparison of the eteplirsen with the historical control is not statistically interpretable.

3.3 Evaluation of Safety

Please see the clinical review.

¹ Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases*. 1976; 29:175–188.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses are not applicable as the study 201 was conducted at a single site in the US and all 12 patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 201 was designed as an exploratory study. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints.

The sample sizes of both Study 201 and the historical control study are very small. The robustness of the study result is a concern since a single patient can change the results substantially. The interpretation of results is also difficult because the sample may not represent the DMD patient population at large. Small studies can be useful for hypothesis generating but usually do not have the ability to provide definitive evidence for a drug's effect.

5.2 Collective Evidence

In Study 201, there was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p=0.958$). Treatment with 30 mg/kg eteplirsen for 24 weeks increased the mean percentage of dystrophin-positive muscle fibers in DMD patients compared to placebo, however, the nominal p value (0.002) can only be considered exploratory due to the lack of multiplicity control.

The MMRM analysis of 6MWT at Week 24 in Study 201 showed a statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo ($p=0.026$). There was no statistically significant difference between the 50 mg/kg eteplirsen group and the placebo ($p=0.563$). These results must be considered as exploratory only.

The open-label extension with historical control is not statistically interpretable.

5.3 Conclusions and Recommendations

The data overall did not provide statistical evidence to support the efficacy in subjects who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

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/s/

XIANG LING
05/03/2016

KUN JIN
05/03/2016
I concur with the review.

HSIEN MING J HUNG
05/03/2016

From: [Guidos, Robert](#)
To: [Woodcock, Janet](#)
Subject: IMPORTANT
Date: Monday, September 19, 2016 5:07:52 PM
Importance: High

From: McClung, Roger (HHS/ASL) [mailto:roger.mcclung@hhs.gov]
Sent: Monday, September 19, 2016 5:06 PM
To: Guidos, Robert
Subject: FW: Inside health piece on Duchenne drug approval

From: McClung, Roger (HHS/ASL)
Sent: Monday, September 19, 2016 5:04 PM
To: Singleton, Sara M. (HHS/ASL); Esquea, Jim (HHS/ASL); Clark, Robert (Bobby) (OS/IOS); Palm, Andrea (HHS/IOS)
Subject: Inside health piece on Duchenne drug approval

Duchenne Drug Approval Reveals Unprecedented Internal FDA Battle Over Patient Role

September 19, 2016

Background documents surrounding FDA's approval of a controversial Duchenne muscular dystrophy drug reveal drug center chief Janet Woodcock, backed by commissioner Robert Califf, made the decision despite strong opposition from the acting chief scientist and a top FDA reviewer, who argued Woodcock was heavily influenced by patient groups and Congress, rather than science. The documents indicate that Woodcock saw the move as an overarching policy shift to offer flexibility on ultra-rare disease treatments, but the review team chief said it set a dangerous precedent for patients.

Califf noted FDA's "understanding about how to include patients in the regulatory process is evolving," and concluded Woodcock did not succumb to pressure from patients, the public, the press or others. But the top reviewer disagreed, saying Woodcock was changing the bar on efficacy and this likely marked the first time a center director overruled a review team on whether effectiveness was demonstrated.

Woodcock, conversely, felt the review team "downplayed and undercut" the views of the patient advocates. But the other officials felt approval of the drug could affect future therapy development, with the review team official describing eteplirsen as "a scientifically elegant placebo," and arguing that approval would send a signal that political pressure and intimidation guide FDA decisions.

The documents reveal there were initial scientific disagreements between the director of the Office of Drug Evaluation-I, Ellis Unger, and Woodcock around the approval of the drug. According to a memo sent to the agency officials from Califf on Friday (Sept. 16), Unger, the review team and Acting Chief Scientist Luciana Borio concluded that the demonstrated levels of dystrophin are not “reasonably likely” to predict clinical benefit.

The memo notes that Woodcock, using “...the greatest flexibility possible for FDA while remaining within its statutory framework,” found eteplirsen is reasonably likely to predict clinical benefit.

“She is clearly employing and interpreting the full range of appropriate information, comprising a 'totality of evidence' approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit,” said Califf.

The dispute was sent to Califf in August by Borio, who chairs the Agency Scientific Dispute Process Review Board (SDR Board). The board was told that under Woodcock's direction, the review team joined her in meetings with patient advocacy groups for DMD on multiple occasions from very early on in the review process.

“The [review team member] described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as 'intense,' 'personal,' and 'intimidating,’” Borio's memo states. Unger thought that Woodcock's early interest and involvement in the approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community to an article published about the initial findings of a study that Unger and Woodcock now agree are misleading and unreliable.

“Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that [Office of New Drugs] has been very conservative in evaluating drugs for accelerated approval,” Borio said.

Unger believed that Woodcock was inclined to grant approval from very early in the process, and a review team member that agreed to speak to the SDR Board anonymously said the review team was never sure whether they were discussing science, policies or politics.

“According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged [Division of Neurology Products] to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the

effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases),” the memo states.

Borio also revealed that the anonymous team member said at least two team members were leaving FDA or had left the agency in the wake of both the decision-making process within the drug center and the pressures exerted by outside forces.

Unger, in a July memo to Office of Scientific Integrity Director G. Matthew Warren, argued the approval of the drug would send the signal that political pressure and even intimidation -- not science -- guides FDA decisions, with extremely negative consequences.

“The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development,” he said.

Borio's memo stated that Unger expressed surprise at the extent of Woodcock's involvement in the advisory committee meeting, adding that she advocated for changing the order of the questions posed to the advisory committee in April and wanted the question on conventional approval to come before the one on accelerated approval. Woodcock allegedly requested a longer than is typical for the open public hearing portion of the meeting as well.

Woodcock told the SDR Board that she thought the review team did a poor job framing the issues during their presentation and that the questions were confusing and poorly worded. She also said that the team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand.

“Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates,” the memo states.

Unger, in a July email to Woodcock, states: “This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed 'reasonably likely to predict clinical benefit.' Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.”

Woodcock told the SDR Board that she was looking at the broader picture for the development of these kinds of drugs for very limited patient

population in the United States.

"She opined that Sarepta in particular 'needed to be capitalized.' She noted that the sponsor's stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would 'lapse into a position of self-treatment,'" the Borio memo states.

Califf said that he was troubled by these statements, but he discussed the issue with Woodcock who maintained her decision was based on science.

"Based on the record and our conversation, I am satisfied that her decision is indeed based on her scientific evaluation of the evidence," he said.

Borio in personal comments to the commissioner noted that there are currently no specific drugs to treat DMD patients and a complete response letter may cause uncertainty on whether eteplirsen would continue to be developed.

"However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions," said Borio.

She also argued that granting accelerated approval for the drug could encourage other developers to seek approval for serious conditions before investing the time and research necessary to establish whether a product is likely to deliver clinical benefit.

Unger's memo states that by allowing the marketing of an ineffective drug, "essentially a scientifically elegant placebo," thousands of patients and their families would be given false hope. He argued this would be unethical and counterproductive. -- *Erin Durkin* (edurkin@iwpnews.com)



IND 077429

ADVICE/INFORMATION REQUEST

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

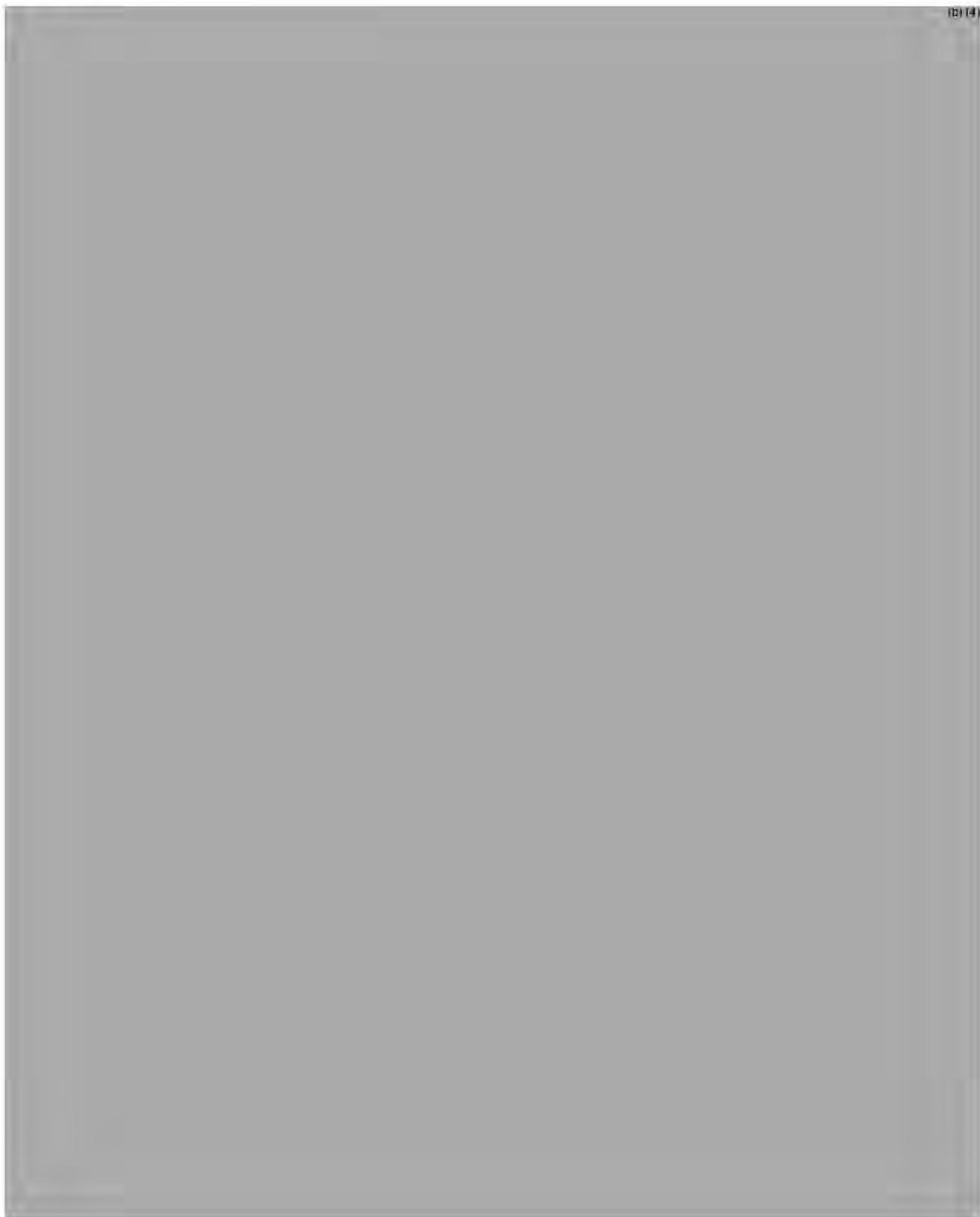
Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen.

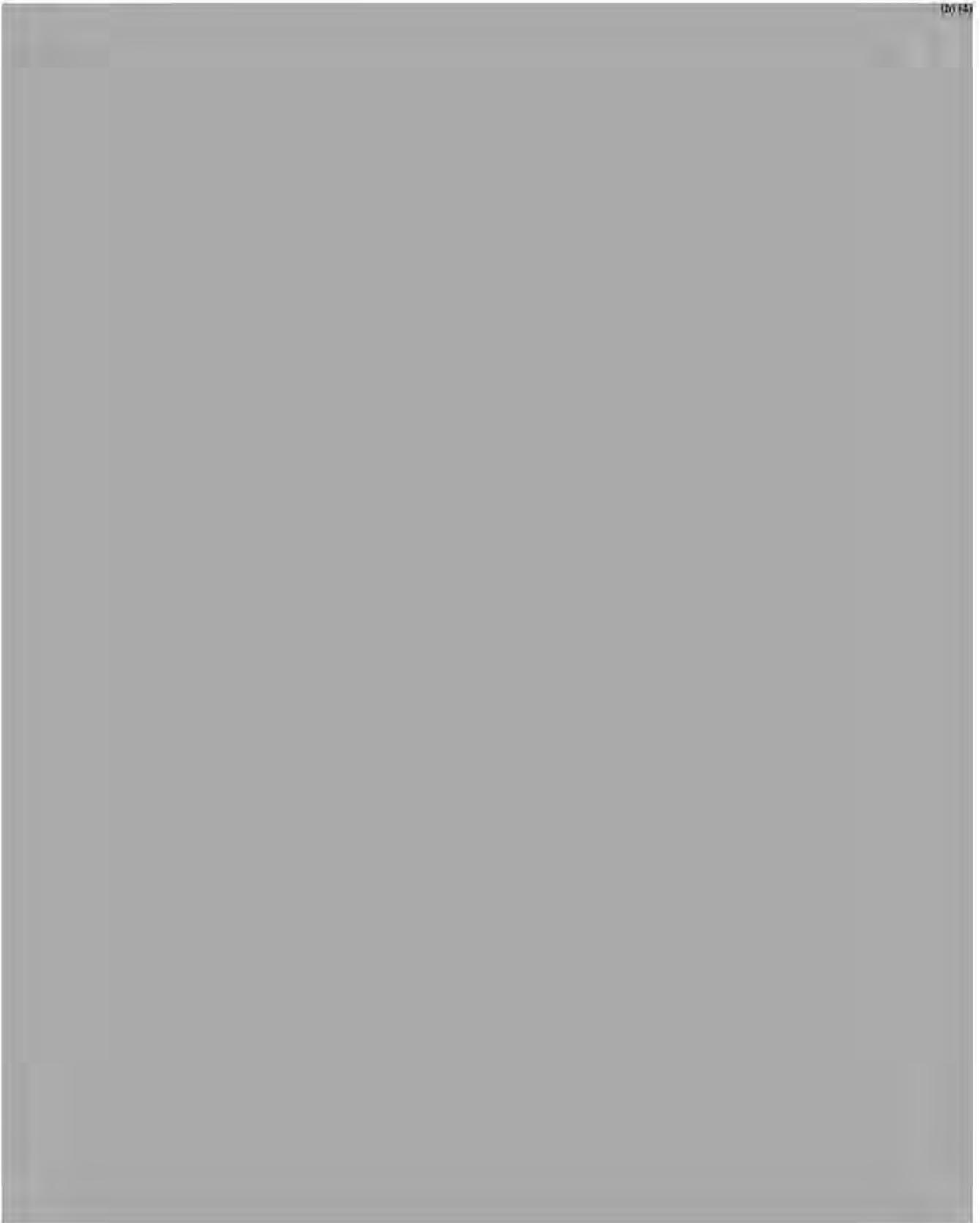
We also refer to the draft clinical protocol for Study

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If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
03/13/2017

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To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: Eteplirsen Coverage: Bloomberg "Sarepta Approval Hints at a Lighter-Touch FDA"
Date: Monday, September 19, 2016 3:20:41 PM
Attachments: [image001.png](#)

Sarepta Approval Hints at a Lighter-Touch FDA

By: Max Nisen

One of the longest and most contentious biotech sagas in recent memory is finally over(ish).

The FDA on Monday granted accelerated approval to Sarepta's drug Exondys, which treats the rare muscle-wasting disease Duchenne Muscular Dystrophy (DMD). The drug could be available to patients before the end of the year. The approval is conditional and can be reversed if a more-rigorous new trial shows the drug doesn't work.

But for now the FDA's decision ends a years-long conflict between scientists and patients. The drug's doubters (yes, including me) had warned there was limited and flawed evidence the medicine worked. The drug's boosters cited a huge unmet need for such a treatment and enough evidence of its effectiveness to justify approving the drug for patients with no options.

The decision could have a major impact beyond DMD patients and Sarepta shareholders, who enjoyed an 86-percent price gain on the news. The market seems to take the drug's approval as evidence the FDA will err on the side of approval in such cases; the Nasdaq Biotech Index rose as much as 1 percent on Monday. Sarepta's fellow DMD drugmaker PTC Therapeutics rose 24 percent.

The approval suggests new medicines might get to market more quickly and on thinner trial results than investors have come to expect. It also bolsters faith that the kind of patient lobbying behind Exondys may be able to shift bureaucratic mountains.

In 2012 Congress gave the FDA extra tools and a mandate to get new drugs for deadly diseases to patients more quickly. The agency appears to be taking that seriously.

Scientists have not been impressed with Exondys. They produced a negative review of the drug in February that cratered Sarepta's shares and left many doubting the drug's chances. An FDA panel of experts voted against letting the drug hit the market. The FDA isn't bound to follow the vote of these panels, but usually does.

But Janet Woodcock, the head of the FDA's Center for Drug Evaluation and Research, overruled the scientists' objections and pushed for the drug's approval, eventually backed by FDA commissioner of food and drugs Robert Califf.

Depending on your point of view, this is either a tragic blow to scientific and statistical rigor, or a victory for patients over myopic bureaucrats with unrealistic expectations.

We'll have to see if this was a one-off -- a unique combination of dire patient need and overwhelming political pressure backing a drug of uncertain effectiveness -- or if there will be many more accelerated approvals based on less-than-ideal studies.

At the very least, Califf's support of Woodcock over the scientists seems like a meaningful hint of where the FDA is leaning under his leadership, which began in February.

There's no doubt the approval is a lifesaver for Sarepta. The company can now sell what will almost certainly be a very expensive drug. And if it follows the playbook other companies have, it is likely to sell more of its now-pricier shares to raise more cash. If the drug had been rejected, then the company's shares likely would have plummeted, and it may have had trouble raising money to continue developing its drug -- something Woodcock worried about openly, according to an FDA document.

At its second-quarter spending rate, Sarepta's cash reserves may have run out early next year without replenishment.

Either way, a previously uncertain door to the market has been opened a crack, and a lot of biotechs are undoubtedly hoping they can squeeze through.

This column does not necessarily reflect the opinion of Bloomberg LP and its owners.

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Subject: Eteplirsen Coverage: Wall Street Journal: FDA Approves Sarepta's Muscular Dystrophy Drug
Date: Monday, September 19, 2016 2:46:54 PM
Attachments: [image001.png](#)

FDA Approves Sarepta's Muscular Dystrophy Drug

Approval comes after panel failed to back drug; Sarepta shares hit multiyear highs

At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their children had benefited from the drug.

By

Thomas M. Burton

The U.S. Food and Drug Administration on Monday gave accelerated approval to the first drug for the crippling disease Duchenne muscular dystrophy, from [Sarepta Therapeutics Inc.](#), **SRPT 93.20 %** after sharp disagreements within the agency.

The circumstances of the approval at the agency were highly unusual, and included sharp internal protests that were ultimately resolved by FDA Commissioner Dr. Robert M. Califf.

An advisory committee to the FDA [in April voted 7-3](#), with 3 abstentions, that the data for the drug weren't enough for agency approval. Specifically, they focused on the fact that the company's hope for approval largely was based on a [single study of 12 patients](#).

On Monday, Sarepta shares surged 88% to \$52.93 after hitting an earlier high of \$56.18, its highest point since March 2002. The stock in April fell as low as \$8 after the FDA panel failed to back the drug, but the price had been rising in recent weeks amid optimism for FDA approval. The gains Monday valued the company at \$2.5 billion.

Duchenne is progressive, severely crippling illness that afflicts male children. It is estimated that it affects about 1 in 3,500 boys world-wide. It destroys muscles and frequently kills patients by the time they are in their 30s.

At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their own children had benefited from taking the drug.

By late May, Sarepta had announced that the FDA [wouldn't make a decision](#) by the deadline and that it would work with the agency in its examination of the data. Before that panel meeting, FDA staffers had indicated they were “prepared to be flexible with respect to a devastating illness with no treatment options.”

An incident at the advisory committee meeting presaged what became an unusually contentious process within the FDA. At the meeting, Dr. Janet Woodcock, director of the FDA's center for drugs, signaled a complex decision lay ahead and said the agency had

“flexibility and that’s where we should take the views of the community into account.” Several doctors who had heard the evidence expressed skepticism then and since that the FDA decision should be anything other than a strict consideration of the very limited evidence.

The agency’s staffers who had studied that evidence concluded that the small study’s design “did not provide interpretable evidence of benefit.”

Ultimately, Dr. Woodcock, a controversial figure within the FDA whom some prominent critics say tends to lean in industry’s direction, decided to approve the drug. Dr. Ellis Unger, a senior physician in the drug division, objected to her decision and filed a protest that reached Dr. Califf, the commissioner.

Dr. Califf, in a decision dated Friday, wrote that he had reviewed the evidence and that his “decision following this review is to defer to Dr. Woodcock’s judgment and authority” to make the decision to approve the drug. The FDA’s acting chief scientist and chair of an FDA committee that resolves internal disputes, concluded the opposite: Dr. Luciana Borio said, according to a memo from Dr. Califf, that she “does not believe the available data and information support accelerated approval of” the drug, which is called eteplirsen.

The approval also comes a week after the FDA confirmed that Dr. Ronald Farkas, who led the FDA review team that evaluated Sarepta’s data, had left the agency.

The FDA said it wouldn’t make any of its staff available for interviews. The decision prompted different reactions from the medical community.

Michael A Carome, director of the Public Citizen Health Research Group, said, “The decision by Dr. Woodcock to approve eteplirsen, against the strong objections of FDA experts who reviewed the drug and the advice of its advisory committee, represents a disturbing disregard for the agency’s legal standards for approving new drugs. In particular, such action eviscerates the FDA’s longstanding requirement that there be substantial evidence of effectiveness for new drugs—even drugs for serious rare diseases—before they are marketed.”

Steven M. Derks, president of the Muscular Dystrophy Association, said, “This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen.”

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Subject: Eteplirsen Coverage: Forbes "Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next?"
Date: Monday, September 19, 2016 4:12:33 PM
Attachments: [image001.png](#)

Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next?

By: Rita Rubin

The Twitterverse was abuzz Monday over the news that the Food and Drug Administration had approved the first drug that could possibly change the course of Duchenne muscular dystrophy, even though an FDA advisory committee had recommended against it.

"This is the day the Duchenne community has been waiting for," tweeted Cure Duchenne, an advocacy group.

"Thx to everyone that (sic) made this happen," tweeted Fight DMD, another advocacy group.

"Majorly HUGE historic moment!!!," tweeted Charley's Fund, yet another such group.

Exondys 51, the brand name of the drug eteplirsen, is far from a cure for the universally fatal disease, abbreviated DMD. The FDA approved it only for boys (DMD rarely affects girls) with the most common type of DMD, seen in just about 13% of patients. And the agency granted approval only on the condition that manufacturer Sarepta Therapeutics of Cambridge, Mass., conduct a trial demonstrating eteplirsen actually improves patients' muscle function, a conclusion that parents of boys who've received the drug as part of a research trial have already reached.

"We are grateful to the many patients and investigators who participated in Exondys 51's clinical studies," Dr. Edward Kaye, Sarepta's interim CEO and chief medical officer, said in a prepared statement. "Exondys 51 represents the culmination of many years of work across our entire organization and the Duchenne community to address a critical unmet need by bringing this novel medicine to patients."

Sarepta is expected to discuss the cost of eteplirsen, administered as a weekly injection, at a conference call beginning at 4 p.m. Eastern time.

DMD patients and parents packed an 11 1/2-hour meeting April 25 of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. Despite the often heart-wrenching testimony they heard, though, only three of the 13 panelists voted "yes" to the FDA's question of whether Sarepta's one study of 12 boys provided "substantial evidence that eteplirsen is effective for the treatment of DMD." Seven voted "no," and three abstained.

Although the FDA usually follows the advice of its advisory committees, the agency decided to

approve eteplirsen via its accelerated approval pathway, which, as the agency describes it, “provides for the approval of drugs that treat serious or life-threatening diseases and generally provide a meaningful advantage over existing treatments.” As was the case with Sarepta and eteplirsen, manufacturers don’t necessarily have to demonstrate that drugs eligible for this program benefit patients, only that they have a favorable effect on a “surrogate endpoint.”

“Surrogate endpoints are used when the clinical outcomes might take a very long time to study or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood,” according to an explanation the FDA posted in July.

DMD is associated with errors in the gene that carries the blueprint for dystrophin, one of a group of proteins that strengthen and protect muscle fibers. The FDA concluded that Sarepta’s data demonstrated an increase in dystrophin production that is “reasonably likely” to translate into improved muscle function in patients. Still, Sarepta needs to prove it, or else, the FDA says, it might withdraw approval.

That wouldn’t happen for at least five years or so, according to letter Dr. Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, sent Monday to Shamim Ruff, senior vice president of regulatory affairs and quality at Sarepta. In the letter, Woodcock laid out the requirements for several postmarket trials of eteplirsen in patients and in rodents.

None of the patients in the postmarket clinical trial designed will be assigned to receive a placebo. As evidenced by testimony by dozens of patients and parents at the advisory committee meeting last spring, the DMD community is already convinced that eteplirsen works, so it likely would have been difficult to recruit volunteers for a study in which they might get a placebo and not the real drug.

Instead of comparing eteplirsen to a dummy injection, Sarepta is supposed to compare the approved weekly dosage of the drug to a “significantly higher” dose, such as one seven times greater. The company has four years in which to complete the trial and another six months after that to submit its final report.

Two rodent studies are supposed to assess whether eteplirsen increases the risk of cancer.

Some observers speculate that FDA decided to approve eteplirsen because the drug’s main critic, Dr. Ronald Farkas, left the agency this month. At the April advisory committee meeting, Farkas questioned the accuracy of the measurements of dystrophin in muscle biopsies from the 12 boys who’d received the drug. And, he noted at the meeting, Sarepta had measured dystrophin in most of the boys before they started treatment, so it wasn’t clear that the levels seen afterward were an effect of the drug. Plus, as the FDA noted in its approval letter to Sarepta, the boys’ dystrophin levels weren’t correlated to how well they could walk.

DMD occurs in one out of every 3,600 baby boys worldwide, according to the FDA. As their muscles weaken, patients often need to use a wheelchair by their early teens, and they typically don’t live beyond their 20s or 30s.

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Subject: Eteplirsen Coverage: Endpoints News "Senior FDA officials warned that eteplirsen OK would lower FDA standards"
Date: Monday, September 19, 2016 4:05:07 PM
Attachments: [image001.png](#)

Senior FDA officials warned that eteplirsen OK would lower FDA standards

By: John Carroll

In the end, Sarepta did many things wrong when it came to developing a new drug for Duchenne muscular dystrophy. But it got one very important part right. The biotech, with the support of a legion of advocates in the patient community, won over Janet Woodcock to their side early on.

The powerful CDER director pushed for an approval even in the face of a heated debate inside the FDA, as senior officials weighed in in opposition to her stand. The acting chief scientist at the agency, Luciana Borio, argued that an approval would lower the agency's standards and encourage other developers to pursue the same kind of lobbying campaigns employed at Sarepta. And she accused Sarepta of acting irresponsibly by knowingly pushing "misleading" information about the drug. Ellis Unger, director of the office of drug evaluation, scoffed at the data Sarepta offered, calling the drug a "scientifically elegant placebo."

But FDA Commissioner Robert Califf refused to overrule Woodcock's decision to OK eteplirsen, despite sharing some of the major objections raised by officials who opposed putting this drug on the market at a price that will likely range in the hundreds of thousands of dollars.

Califf's summary review of the extraordinary showdown over eteplirsen point to problems that would have easily killed practically any other marketing application. But with the center director taking a passionate stand in favor of the drug, the commissioner says he decided that he would defer to Woodcock in view of his lack of technical expertise in the matter and a sufficient record of evidence to warrant its move into the market.

Both Unger and Borio opposed Woodcock's decision to grant an accelerated approval for eteplirsen, according to the September 16 memo from Califf as well as their own memos. Califf set out to determine if the FDA was significantly lowering the bar for an approval, but ultimately decided that Woodcock was pursuing a well established track record for being willing to take tough, ethical stands inside the agency, rather than buckling to a lobbying campaign.

According to Borio, who says that Woodcock was leaning toward an OK in 2014, an approval of this flawed application may set a dangerous precedent that will encourage desperate patients to mount a furious assault in favor of other drug approvals. Her position, outlined in the memo:

"Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies — both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for

serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients.”

Unger, who warned that the safety profile of eteplirsen is not yet known and that patients taking the drug could die from treatment, was scathing in his assessment of the therapy.

By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

And the review documents included Woodcock’s extraordinary argument that Sarepta needed an accelerated approval to help its stock price, so it could fund additional work.

She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

Significant deficiencies in the eteplirsen program, says Califf, include a consensus that “the poor quality of many of the biopsies and the failure of the sponsor to implement a high-quality procedure for assay validation” made it impossible to consider much of the data in the application. They all agreed that the drug produced levels of dystrophin that were “small compared with expectations at the outset of trials in humans.”

Sarepta “touted” a study that used unreliable measures of the assay, leading the company to overstate protein expression in follow-up biopsies. That study was debunked by FDA experts, Califf says, and should be corrected or retracted. Borio was much more critical of Sarepta. Her memo states:

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202147 – which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings.

There is a distinct possibility, the FDA feels, that increasing the dose would provide enough dystrophin expression, the key biomarker for this disease, to make it work as hoped. But it’s only been tested in animals, never in humans – at least not yet.

And if Sarepta had done what the FDA was telling the company to do, says Califf, then they would probably already have enough compelling data in hand to make a decision based on the merits of the drug.

Woodcock actually decided in favor of an approval on May 4, after taking an “extensive and early involvement” on the drug, which raised concerns about interference with “the integrity of scientific reviews” at lower levels in the FDA. Woodcock completed her final memorandum before Unger had had a chance to complete his own.

Once she determined her position, Woodcock never budged. Ultimately, that was enough. Whatever else happens, Woodcock was proved right about Sarepta’s stock price. Shares are up 86% in mid-afternoon trading.

Fallon Smith

Press Officer

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From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: Eteplirsen Coverage: STAT "Behind the Sarepta drug approval was intense FDA bickering"
Date: Monday, September 19, 2016 3:26:59 PM
Attachments: [image001.png](#)

Behind the Sarepta drug approval was intense FDA bickering

By: Ed Silverman

The run-up to Monday's approval of a Sarepta Therapeutics drug to treat Duchenne muscular dystrophy was marked by unusual bickering inside the Food and Drug Administration, where debate over a key scientific question morphed into a formal dispute, and the head of the drug review division was accused of being too intensely involved in the process for evaluating the medicine.

Ultimately, the decision to greenlight the drug fell to the FDA Commissioner, Dr. Robert Califf. In a 12-page memo last Friday, he deferred to Dr. Janet Woodcock, the controversial head of the drug review division, who pushed hard to approve the Sarepta medication but clashed with other FDA officials along the way.

"The science is not in dispute beyond the usual types of disagreement that occur when experts review clinical evidence from different perspectives," he wrote. "It is clear that Dr. Woodcock's decision utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening decisions of the disease and the lack of alternative treatments."

Califf was compelled to chronicle his decision in response to a formal dispute that was filed by Dr. Ellis Unger, who reports to Woodcock, and disagreed with her decision to approve the drug and the way she went about advocating for approval. The Califf memo was one of several internal FDA documents involving the dispute and the fate of the Sarepta drug that were released Monday.

There is frequently disagreement among FDA staff over the extent to which clinical trial data should support the approval of a new medicine. But the intensity of the dispute surrounding the Sarepta drug underscores the stakes that were involved in this episode. Beyond this one drug, the discord among FDA officials illuminated a wider debate about the pressures the agency faces to endorse medicines from an increasingly aggressive patient population.

In his dispute, Unger identified four deviations from the usual typical decision-making process. He claimed Woodcock was involved in the early stages of the review; she had "extensive involvement" in planning and participating in an expert panel meeting last spring; she made an initial decision last May to approve the drug before the FDA review team completed a draft review memo; and she issued a final decision memo before Unger finalized his own memo.

Unger was not alone. In an Aug. 8 memo to Unger, Dr. Luciana Borio, the FDA acting chief scientist who convened the board that reviewed the dispute, wrote that "we fear that those actions could

have chilled scientific debate within (the FDA Center for Drug Evaluation and Review) and reduced the level of participation by the review team during the final stages of the decision-making process.”

“Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages,” Borio wrote. And she noted that at least two staffers were leaving or were about to leave in response to the decision-making process “and the pressures exerted by outside forces.”

Indeed, the dispute centered primarily on a disagreement over whether the Sarepta drug would produce enough of a protein called dystrophin to generate a clinically meaningful benefit. Boys suffering from Duchenne have a mutation and lack the protein. Sarepta argued that a very small clinical trial demonstrated the drug helped enough boys based on various measures, including a six-minute walking test.

According to the memos, Woodcock acknowledged some issues with trial data submitted by the company to win approval, but she disagreed with Unger and other FDA staff about the extent to which boys treated with the medicine would experience a meaningful clinical benefit.

Their disagreement, however, also reflected a more fundamental debate over the stance the agency should take toward the Sarepta drug. Until now, the FDA had not approved a drug to treat Duchenne, prompting parents and some lawmakers to argue for accelerated approval, a process that relies on surrogate endpoints instead of actual medical benefits to endorse a drug.

This has been a highly charged issue and has transformed the Sarepta drug into a litmus test for agency approval of new medicines, notably for diseases with unmet medical needs. Seen through that prism, Unger maintained that approving the drug would be detrimental to the FDA approval process on a long-term basis.

“By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk,” he wrote in a July 18 dispute report. “I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.”

According to Borio, both Unger and the members of the FDA review team told the dispute review board that Woodcock “seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy.”

Eteplirsen is the name of Sarepta’s DMD drug that was approved by the FDA on Monday.

Ultimately, the review board found that “Woodcock’s extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and

decision-making process. Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages.”

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Subject: Eteplirsen Coverage: Forbes and US News and World report
Date: Monday, September 19, 2016 3:12:56 PM
Attachments: [image001.png](#)

Forbes: Sarepta Wins FDA Nod For Embattled DMD Drug -- But With A Catch

By: Arlene Weintraub

Just five days after its main nemesis at the FDA departed the agency, Sarepta Therapeutics has won a long-sought-after approval for eteplirsen, its drug to treat Duchenne muscular dystrophy (DMD). It's been a long, strange trip for the Cambridge, Mass.-based company, which has held strong support from the DMD community but endured everything from a freak snowstorm that delayed an FDA advisory committee review to the aforementioned critic, Ron Farkas, who seemed to be doing everything in his power to prevent eteplirsen from getting approved.

But despite the good news—which prompted Sarepta's shares to nearly double to \$54.30 on Monday—the approval isn't entirely straightforward for the drug, which will carry the trade name Exondys 51. In a statement, the FDA said it is requiring Sarepta to perform another clinical trial to prove the drug does what the company claims—namely that it improves motor function in DMD patients who have a particular mutation in a gene that produces dystrophin, a protein key in proper muscle function.

Exondys 51 was cleared for marketing under the FDA's accelerated approval process, which generally requires that companies provide additional proof of efficacy. If Sarepta's drug fails the trial, the FDA can withdraw the approval, the agency says. Sarepta has not yet responded to the FDA's approval notice.

In a statement, Edward Kaye, M.D., Sarepta's interim chief executive officer and chief medical officer, said the approval "represents the culmination of many years of work across our entire organization and the Duchenne community to address a critical unmet need by bringing this novel medicine to patients." The company did not provide details about additional trials, nor did it disclose pricing of the new drug, though it was planning a conference call for later in the afternoon, when those questions were bound to be asked.

Doubts that Sarepta would ever reach this milestone emerged in late January, when the FDA released briefing documents ahead of a scheduled advisory panel meeting on Exondys 51. The documents blasted the company for basing its approval application on a trial with only 12 patients. To measure the drug's effect, the investigators performed a six-minute walk test on the trial participants, but the FDA advisors—led by Farkas—said the test revealed "no nominally significant difference" between patients taking a higher dose, a lower dose or a placebo.

Sarepta responded by releasing updated data showing that 10 of the patients who were taking the drug were still walking 216 weeks after their entry into the trial. Dozens of DMD patients, parents and physicians were set to travel to D.C. for the meeting when a massive snowstorm hit, delaying

the gathering until late April.

After a day filled with emotional testimonies from patients and parents, the panel voted 7-6 against approval. The FDA doesn't have to follow the advice of its advisory panels, but it usually does. When it missed the scheduled May 26 deadline for approving Exondys 51, speculation that the drug was doomed soared. In June, the FDA asked for a bit more data on the small trial that had already been submitted, but after that, there was little news indicating what the future of the drug might be.

But then the news of Farkas' departure emerged on September 14, sending Sarepta's shares up 27% in a day.

Exondys 51 is based on a technology platform called "exon skipping," which enables the production of a synthesized form of dystrophin that's designed to function like the original muscle-preserving protein.

The DMD community rejoiced in the hours following the approval. "The first FDA-approved treatment for Duchenne is a landmark in our fight against this disease. It provides hope for all Duchenne families," said Debra Miller, founder and CEO of CureDuchenne, which provided early funding for the eteplirsen trials. "Boys on eteplirsen have experienced improvements in quality of life that are amazing for a progressive disease that has remained without an approved drug for so long."

The next challenge for Sarepta will be completing a second trial of the drug that will satisfy the FDA. It won't be easy: DMD is a rare disease that affects 20,000 patients per year, most of them boys. And only about 13% of DMD patients have the mutation that Exondys 51 targets, according to Sarepta.

This post has been updated with statements and details from the company and from CureDuchenne.

###

US News: Controversial Drug OKd for Duchenne Muscular Dystrophy

By: Kimberly Leonard

The Food and Drug Administration on Monday approved the first drug to treat Duchenne muscular dystrophy, a rare and devastating genetic disease that causes patients to lose control of their muscles.

The decision comes after months of delay as the FDA pressed the drug's manufacturer – Cambridge, Massachusetts-based Sarepta Therapeutics – to provide more evidence that its treatment worked. Sarepta had provided evidence from only 12 patients and did not use a controlled trial that involved the use of a placebo.

The FDA went against the advice of a panel that in April recommended against the drug's approval, citing insufficient evidence.

The injected drug, called Exondys 51, or eteplirsen, contains side effects like vomiting and problems with balance. It has been granted fast-track approval, meaning that the FDA has decided a drug company provided enough evidence that a drug may work but does not guarantee it. As a condition of the approval, Sarepta must conduct a two-year randomized trial and report back to the agency on its findings.

Parents of children with the disease have been lobbying the FDA to approve the drug. Duchenne is the most common type of muscular dystrophy, and typically affects boys. It causes progressive muscle deterioration and weakness because children who have it lack the protein dystrophin, which keeps muscle cells intact. By the time children reach their teenage years, they typically need a wheelchair, and as they get older they struggle with heart and breathing conditions, and many die when they hit their 20s and 30s.

The additional testing FDA is requiring will help determine whether children can move better as a result of taking eteplirsen, and if the FDA determines the evidence isn't sufficient then it may withdraw its approval. About 13 percent of children with Duchenne have a specific gene mutation that could allow the drug to be helpful to them by restoring the way that their cells read dystrophin, potentially slowing or preventing the disease. In a study Sarepta provided to the FDA, the dystrophin levels for children who were tested increased by only 0.9 percent after 3.5 years, which is about the same rate as children who had not taken the drug.

"Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease," Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said in a statement. "In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders. Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval."

Frank Burroughs, president of the Abigail Alliance, which advocates for greater access to developing drugs, sent a letter to Woodcock Monday after the FDA's announcement saying, "This drug should have been approved three plus years ago, when Duchenne patient advocates ... started pushing for its approval!" He pointed to 29 other drugs that the Abigail Alliance has pushed for access to, saying they all ended up being approved by the FDA.

Others have been critical of the way the drug has been considered, saying that scientific evidence is necessary before a drug is made available to the public.

In a release about the FDA's decision, the agency said it had considered the "potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy."

Sarepta Therapeutics' shares surged briefly by more than 80 percent after the FDA's announcement.

Fallon Smith

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From: [Jarow, Jonathan](#)
To: [Woodcock, Janet](#)
Subject: FW: Approval of first drug for Duchenne muscular dystrophy
Date: Monday, September 19, 2016 2:32:19 PM

Very well written.

Thank you,
Jonathan

From: CDER Center Director
Sent: Monday, September 19, 2016 10:01 AM
To: FDA-CDER-wide
Subject: Approval of first drug for Duchenne muscular dystrophy

CDER Staff:

Today, FDA approved the first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children. The drug, Exondys 51 (eteplirsen) injection, is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Exondys 51 was approved under the accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy. Accelerated approval is based on data that shows the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement.

While accelerated approval provides earlier patient access to promising new drugs, under its provisions FDA requires the sponsor to conduct clinical trials to verify the predicted clinical benefit of the drug. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to show that the drug preserves motor function.

The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework. In this case, flexibility is warranted because of 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 life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway.

In June 2015, FDA issued a [draft guidance](#) for industry on developing drugs for the treatment of DMD and related dystrophinopathies – one year following our receipt of a proposed draft guidance for consideration from the advocacy group, Parent Project Muscular Dystrophy (PPMD). This effort highlights how collaboration between engaged stakeholders and FDA can contribute to drug development. We appreciate PPMD's tireless efforts, and value their and the DMD community's input.

FDA held an [advisory committee meeting](#) on April 25, 2016 to discuss the marketing application for this drug. The advisory committee recommended that there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. The AC also voted 7-6 against accelerated approval, because of uncertainties about the dystrophin data presented by the sponsor. Subsequently, the sponsor submitted additional data showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level.

I would like to acknowledge the work done by the review team. The effort spent to evaluate the application data and scientific discussions are much appreciated.

We will continue to work with sponsors to facilitate the development and approval of effective treatments for DMD and other rare diseases.

For more information about DMD, and today's approval, visit [the press release](#).

Janet Woodcock

From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: Eteplirsen Coverage: Muscular Dystrophy Association "MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy"
Date: Monday, September 19, 2016 12:34:24 PM
Attachments: [image001.png](#)

MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy

The Muscular Dystrophy Association today celebrated news of the U.S. Food and Drug Administration's decision to grant accelerated approval for eteplirsen, the first disease-modifying drug to treat the most common childhood form of muscular dystrophy.

Accelerated approval of the drug, which will treat a subset of those living with Duchenne muscular dystrophy, is an important step forward in the development of therapies for neuromuscular diseases and marks an historic achievement for the entire DMD community.

"Today has been a long time in the making," said MDA President and CEO Steven M. Derks. "This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen. Throughout this process we have seen the undeniable strength of our community to rally behind MDA's commitment to find treatments for our families. This is an important victory, and we are honored to stand shoulder-to-shoulder with everyone who has fought to make this day a reality."

Approval to market eteplirsen was given to pharmaceutical company Sarepta Therapeutics. Eteplirsen will be the first disease-modifying drug on the market in the United States to treat DMD, and approximately 13 percent of DMD patients potentially may be eligible for treatment. Under the terms of the FDA's accelerated approval, Sarepta must conduct a clinical trial of eteplirsen to confirm clinical benefit.

The news comes following an historic turnout at the FDA's advisory committee hearing in April, which brought a record-breaking number of families, members of the medical community and supporters to Washington to testify on behalf of the DMD community in favor of treatment options for Duchenne.

MDA Executive Vice President and Chief Medical and Scientific Officer Valerie A. Cwik, M.D., provided compelling oral testimony at the hearing, in addition to other MDA appeals to the FDA, urging the agency to consider the totality of the data and utilize maximum regulatory flexibility in its review of the drug.

"For our families, therapy options can't come soon enough," Cwik said. "MDA is eager for this treatment to get into the hands of those whom it can help, forever grateful to our partners, supporters, and, most importantly, our families, who all helped turn hope into a treatment that can change the course of Duchenne. We fully expect this accelerated approval will be an inspiration and

a catalyst to more innovation and follow-on funding for drug development across the board."

MDA has invested more than \$200 million in DMD research and has been central to the development of the exon skipping approach from the beginning in the 1990s, having funded foundational work upon which the strategy was built as well as extensive research into the strategy since that time. MDA supported the early development of eteplirsen via funding to Steve Wilton, then at the University of Western Australia in Perth, who pioneered the exon skipping technique that allows eteplirsen to work.

This year, MDA already has committed more than \$17 million to research, as it takes a unique big-picture perspective across the spectrum of muscle-debilitating diseases that take away everyday abilities such as walking, talking and hugging. With the help of its supporters, MDA plans to double its research spend targeting treatments and clinical trials by the year 2020.

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Subject: Eteplirsen Coverage: Inside Health Policy "FDA Goes Against Advisory Committee, Approves Duchenne Drug"
Date: Monday, September 19, 2016 12:16:54 PM
Attachments: [image001.png](#)

FDA Goes Against Advisory Committee, Approves Duchenne Drug

By: Erin Durkin

FDA granted accelerated approval to a controversial Duchenne muscular dystrophy drug Monday (Sept. 19) after an emotional hearing in April where an advisory panel voted against approval of the drug causing a backlash from an audience of DMD patients, parents, doctors and advocates. Agency officials had left the door open in April to approve the drug based on testimony from patients and their parents, leading some to view the product as a test for how much flexibility FDA has to weigh patient testimony regarding medical need.

In a memo to FDA staff Monday, drug center chief Janet Woodcock said Sarepta Therapeutics submitted additional data after the advisory committee meeting.

The agency is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The study will assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. "If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug," FDA said in a press release.

Woodcock said in April that it would be appropriate to consider patient testimony. "I think that's fair," Woodcock said. "The standard is adequate and well-controlled trials. That's in the statute. We are instructed in flexibility on how to interpret that based on medical need."

At the time, Billy Dunn, director of the Division of Neurology Product in FDA's drug center, also signaled the agency would seriously consider the patients' testimony.

"The emotion and passion in the room during the discussion is clear, and I mentioned at the beginning of the day that we listen and we listen carefully. While I recognize there's great concern about the discussion and the results of the votes, I assure we listened very carefully to some very meaningful testimony today. We've observed the panel be highly influenced by that testimony. I assure that we will take the information we learned here today under very serious consideration as we adjourn this meeting," said Dunn.

FDA had delayed its decision on the drug in May, according to the drug maker Sarepta Therapeutics, while lawmakers questioned the agency over how it ran the advisory committee that voted against approval of the product.

GOP Sens. Ron Johnson (WI) and Dan Coats (IN) wrote to FDA that they were concerned with how the agency posed questions to the advisory committee, alleging the questions were framed in a

way that made it difficult for members to vote in favor of the application being approved. -- Erin Durkin (edurkin@iwppnews.com)

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Subject: Eteplirsen Coverage: Politico and Wallstreet Journal
Date: Monday, September 19, 2016 11:19:56 AM
Attachments: [image001.png](#)

Politico: FDA approves muscular dystrophy drug pushed by lawmakers

By: Sarah Karlin-Smith

FDA granted [accelerated approval](#) to Sarepta's Duchenne muscular dystrophy treatment this morning, following months of political pressure by lawmakers and patient advocates. FDA's drug center Director Janet Woodcock, with the support of Commissioner Robert Califf, overruled the drug's review team, which had raised concerns about the drug's effectiveness, according to documents posted on FDA's website. Ellis Unger, the director of the Office of Drug Evaluation I and FDA's chairman of the scientific dispute process review board, also recommended against approval.

The agency's green light makes eteplirsen the first drug approved for the rare genetic disease that often causes death in patients' 20s or 30s.

The approval follows a [negative review from a FDA advisory committee](#) meeting for the drug in April, when agency advisers said Sarepta had not provided "substantial evidence" that the drug effectively treats the disease. FDA's own briefing documents issued ahead of the panel indicated the agency also was not convinced the drug warranted approval.

The FDA's accelerated approval means it concluded eteplirsen is reasonably likely to improve patients' lives or longevity. Sarepta will have to conduct an additional clinical trial as a condition of full approval to confirm the drug's clinical benefit. If that fails, FDA can withdraw the drug's approval.

More than 100 members of Congress have pushed FDA to approve the drug, delivering floor speeches and writing op-eds. FDA appropriations bills passed by House and Senate committees in the spring also included report language reminding the agency it has "the tools, authorities and latitude necessary" to approve rare-disease treatments like drugs for Duchenne as fast as possible.

###

WSJ: Sarepta Wins FDA Approval for Duchenne Drug

By: Tom Burton

The Food and Drug Administration gave accelerated approval to the first drug for the crippling disease Duchenne muscular dystrophy, from Sarepta Therapeutics Inc.

The circumstances of the approval at the agency were highly unusual. First, an advisory committee to the FDA last April voted 7-3, with 3 abstentions, that the data for the drug weren't enough for agency approval. Specifically, panel members focused on the fact that the company's hope for approval largely was based on a single study of 12 patients.

Sarepta's stock shot up 75% Monday to \$49.27 in midmorning trade. The stock has more than doubled in the past three months. The stock has more than doubled in the past three months.

Duchenne is progressive, severely crippling illness that afflicts male children. It is estimated that it affects about 1 in 3,500 boys world-wide. It destroys muscles and frequently kills patients by the time they are in their 30s.

At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their own children had benefited from taking the drug.

By late May, Sarepta had announced that the FDA wouldn't make a decision by the deadline and that it would work with the agency in its examination of the data. Before that panel meeting, FDA staffers had indicated they were "prepared to be flexible with respect to a devastating illness with no treatment options."

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**U.S. FOOD & DRUG
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Subject: Eteplirsen Coverage: Reuters, The Street and CNBC
Date: Monday, September 19, 2016 10:37:39 AM
Attachments: [image001.png](#)

Reuters: Sarepta's keenly watched muscle dystrophy drug wins FDA approval

By: Natalie Grover

Sarepta Therapeutics Inc's Duchenne muscular dystrophy drug won approval from the U.S. Food and Drug Administration on Monday, capping months of regulatory uncertainty and pressure from parents and patient advocates to endorse it.

The drug, eteplirsen, is designed to treat a subset of patients with Duchenne's, a rare, progressive genetic disorder that hampers muscle movement, eventually killing most sufferers by the age of 30.

The injection was given accelerated approval, which means the company is still required to provide more data to verify the drug's predicted clinical benefit.

The FDA said on Monday that Sarepta was required to conduct a trial to confirm the drug's effectiveness, without which the regulator may withdraw approval. (bit.ly/2cCad2V)

Until now there have been no FDA-approved drugs for DMD, and pressure has been increasing on the regulator to swiftly approve treatments.

###

The Street: Sarepta Wins Approval for Duchenne Drug After Long FDA Review

By: Adam Feuerstein

The first drug to treat the underlying cause of Duchenne muscular dystrophy, developed by Sarepta Therapeutics (SRPT), secured marketing approval from the U.S. Food and Drug Administration, the FDA announced Monday.

Sarepta, its shareholders, biotech investors, and Duchenne patients and their families have been waiting years for today's news.

Nothing about the clinical and regulatory path taken by eteplirsen, the scientific name for the Sarepta drug, has adhered to the conventional biotech drug development playbook. The FDA's affirmative approval decision announced today emerged from a volatile and controversial review process that took an interminable 14 months to complete.

But that's all history now. Eteplirsen, rebranded as Exondys, is approved for sale in the U.S. Within

days, Duchenne patients will have access to a drug which slows the progressive weakening of their muscles that is a hallmark of the rare, inherited disease.

And investors will now turn their attention to forecasting future Exondys sales instead of debating if the drug will ever (or should) reach the market.

Sarepta shares were halted Monday after the stock spiked 77% to \$50.07.

The FDA letter confirming Exondys' approval can be read [here](#).

"Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in a statement. "In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders. Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval."

The FDA is requiring Sarepta to conduct a follow-on study to confirm the ability of Exondys to improve motor function in Duchenne patients. If this study fails, FDA could remove Exondys from the market.

The company has not yet announced Exondys pricing but it's believed the drug could cost \$400,000 to \$500,000 per year.

There are approximately 25,000 to 30,000 Duchenne patients in the U.S. and Europe, but only 13% of them, or roughly 3,500 patients, carry the specific genetic mutation which can be treated with Exondys.

Of those 3,500 eligible Duchenne patients, approximately 1,400 reside in the U.S., estimates Baird analyst Brian Skorney. This will be the initial commercial opportunity for Sarepta with Exondys.

Duchenne muscular dystrophy is a rare, genetic disease caused by a mutation on the X chromosome. This mutation, in turn, results in malfunctioning or missing dystrophin, a protein necessary for proper muscle function. Boys with DMD (the disease almost always strikes boys) suffer from progressive weakening of their muscles. By around 12, they can no longer walk. The disease also affects breathing and heart function. Few DMD patients live beyond 30.

Since DMD is caused by a mutation in the gene encoded to make dystrophin, one approach to treating the disease is to design a drug capable of removing or "skipping over" the damaged section, or exon, of the gene. Doing this allows the gene to produce dystrophin that is partially functional and stabilizes muscle function. This is how Exondys works.

###

CNBC: Sarepta shares briefly leap 80% after FDA approves drug

By: Evelyn Cheng

Shares of Sarepta Therapeutics briefly surged more than 80 percent in Monday morning trade after the U.S. Food and Drug Administration approved its muscular dystrophy drug eteplirsen.

The drug is the first approved to treat patients with Duchenne muscular dystrophy, a rare, genetic muscle-wasting disease, and was given accelerated approval, the FDA said.

Earlier, the stock climbed about 11 percent before trading was temporarily halted. Recently, the stock changed hands up 60 percent, or a 21 percent gain for the year so far.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
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From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: Eteplirsen Coverage: Business Insider and Bloomberg
Date: Monday, September 19, 2016 10:27:46 AM
Attachments: [image001.png](#)

Business Insider: Biotech stock explodes 80% after the FDA approves the first drug to treat a rare muscle disorder

By: Akin Oyedele

Sarepta Therapeutics shares spiked by as much as 86% in trading on Monday after the US Food and Drug Administration said it approved a key drug.

The FDA approved Exondys 51 (eteplirsen), the first such drug to treat patients with Duchenne muscular dystrophy (DMD), it said in a statement.

DMD is a rare disorder caused by the absence of dystrophin, a protein that helps keep muscle cells intact, and causes gradual but severe damage while limiting movement. Patients could need wheelchairs even in their early teens, and could die by the time they are in their 30s.

The FDA confirmed that Dr. Ronald Farkas, a key staffer who opposed the drug had left the agency, Stat News reported on Friday. Sarepta shares soared then, as Farkas' departure was seen by investors to pave the way for approval.

"Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in the statement.

###

Bloomberg: Sarepta Wins Approval for Duchenne Drug After Long FDA Review

By: Anna Edney

Sarepta Therapeutics Inc. won U.S. approval for its drug to treat Duchenne muscular dystrophy, a victory for young patients with a form of the deadly muscle disease and their parents who were devastated in April when a panel of outside advisers recommended against clearing the product.

The Food and Drug Administration said the drug, which will be sold as Exondys 51, needs more study to prove that it actually helps patients. It was approved under the agency's "accelerated approval" program, which can make drugs available for sale if they show signs they might help patients while more study is conducted.

“Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval,” Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, said in a statement.

Sarepta shares surged 75 percent to \$49.28 at 10:04 a.m. in New York, the biggest intraday gain since October 2012. The gain gives Cambridge, Massachusetts-based Sarepta a market value of about \$2.4 billion, and the positive FDA news could make it a much more appetizing -- and expensive -- takeover target.

Long Process

The approval, announced on the FDA’s website, comes after the agency asked Sarepta for data from patient biopsies obtained in an ongoing, incomplete study of the drug that was intended to confirm its benefit after it reached the market. The request was a rare step by the agency, which has given more weight to patient perspectives even when clinical trials don’t conclusively show benefit.

Duchenne muscular dystrophy, or DMD, is a genetic disease that mainly affects young boys in which the body lacks a protein, called dystrophin, that keeps muscles intact. Patients quickly lose strength, robbing them of the ability to walk, stand and breathe. Sufferers often die by age 25, usually from lung disorders, according to the National Institutes of Health.

Fallon Smith

Press Officer

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From: [Rosenberg, Amy](#)
To: [Woodcock, Janet](#)
Subject: FW: Approval of first drug for Duchenne muscular dystrophy
Date: Monday, September 19, 2016 10:13:56 AM

I'm proud of you!

From: CDER Center Director
Sent: Monday, September 19, 2016 10:01 AM
To: FDA-CDER-wide
Subject: Approval of first drug for Duchenne muscular dystrophy

CDER Staff:

Today, FDA approved the first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children. The drug, Exondys 51 (eteplirsen) injection, is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Exondys 51 was approved under the accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy. Accelerated approval is based on data that shows the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement.

While accelerated approval provides earlier patient access to promising new drugs, under its provisions FDA requires the sponsor to conduct clinical trials to verify the predicted clinical benefit of the drug. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to show that the drug preserves motor function.

The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework. In this case, flexibility is warranted because of 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 life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway.

In June 2015, FDA issued a [draft guidance](#) for industry on developing drugs for the treatment of DMD and related dystrophinopathies – one year following our receipt of a proposed draft guidance for consideration from the advocacy group, Parent Project Muscular Dystrophy (PPMD). This effort highlights how collaboration between engaged stakeholders and FDA can contribute to drug development. We appreciate PPMD's tireless efforts, and value their and the DMD community's input.

FDA held an [advisory committee meeting](#) on April 25, 2016 to discuss the marketing application for this drug. The advisory committee recommended that there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. The AC also voted 7-6 against accelerated approval, because of uncertainties about the dystrophin data presented by the sponsor. Subsequently, the sponsor submitted additional data showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level.

I would like to acknowledge the work done by the review team. The effort spent to evaluate the application data and scientific discussions are much appreciated.

We will continue to work with sponsors to facilitate the development and approval of effective treatments for DMD and other rare diseases.

For more information about DMD, and today's approval, visit [the press release](#).

Janet Woodcock

From: oasfda@fda.gov
To: Woodscock, Janet
Subject: Pending Signature - NDA 206488 Accelerated Approval (COR-NDAACTION-04)
Date: Monday, September 19, 2016 8:36:24 AM



[Proceed to DARRTS Welcome Screen](#)



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DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT** send this page with the letter.

Application #(s):	NDA 206488
Communication Type:	Correspondence
Communication Group:	NDA Action
Communication Name:	Accelerated Approval
Communication ID:	COR-NDAACTION-04
Drafted by:	Choy, Kelley, Ware 9/16/16
Clearance History:	M Chelliah / Heimann (CMC) 6/24/16, 6/30/16; Yasuda/Hughes 6/28/16, Yasuda 7/20/16, 8/8/16, 9/16/16; SRT 6/30/16, 7/18/16, 7/19/16; Locicero 7/1/16; Bastings 7/1/16, 9/16/16; J Woodcock
Finalized:	
Filename:	
Signatory Authority:	NMEs and 351(a) BLAs must be signed by the Office Director or Deputy Office Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use when approving an NDA under 21 CFR 314.510 (approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity).
Notes:	

Version: 02/11/2016

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA 206488

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We acknowledge receipt of your major amendment dated January 8, 2016, which extended the goal date by three months.

This new drug application provides for the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206488.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, we refer to your June 10, 2016, submission in which you commit to implement the carton container label revisions requested in our June 6, 2016, correspondence. Specifically, you agree to remove the reference to the compendial grades from the carton labels at the time of next printing, but no later than 120 days post-approval, and to notify us of this change via submission of a "Changes Being Effected" supplemental application.

PRODUCT QUALITY

Based on evaluation of the stability data provided, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°C).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number: PRV NDA 206488. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of

times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2016. This requirement, along with required completion dates as agreed upon on September 16, 2016, is listed below.

- 3095-1 In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Draft Protocol Submission: 10/2016
Final Protocol Submission: 04/2017
Trial Completion: 11/2020
Final Report Submission: 05/2021

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocol to your IND 077429 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity or an unexpected serious risk of immunogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3095-2 A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2016
Final Protocol Submission:	03/2017
Study Completion:	04/2020
Final Report Submission:	06/2020

- 3095-3 A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2016
Final Protocol Submission: 01/2017
Study Completion: 05/2018
Final Report Submission: 06/2018

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies.

- 3095-4 A study to evaluate:

1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2017
Final Protocol Submission: 08/2017
Study Completion: 12/2017
Final Report Submission: 02/2018

Additional guidance for immunogenicity assay development, though more specific for therapeutic protein products, may be found in the draft guidance: "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products"

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocols prior to initiation of the studies.

Submit the protocols to your IND 077429, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-5 Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2016
Final Protocol Submission: 04/2017
Trial Completion: 04/2021
Final Report Submission: 10/2021

A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-6 Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

- 3095-7 Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) results that were observed at lot release.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

Submit clinical protocols to your IND 077429 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic

License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

(b) (5)

6 pages of draft language have been withheld as b(5) immediately following
this page

From: [Dunn, Billy](#)
To: [Unger, Ellis](#); [Bastings, Eric](#); [Choy, Fannie \(Yuet\)](#); [Kozauer, Nicholas](#); [Yasuda, Sally](#); [Hughes, Alice](#); [Ware, Jacqueline H](#)
Cc: [Woodcock, Janet](#)
Subject: Sarepta approval letter
Date: Friday, September 16, 2016 9:18:47 AM

Folks,

Dr. Woodcock contacted me this morning interested in moving forward with signing the approval letter in hard copy today. She is copied on this email. Could folks, consulting with Ellis, work on getting Dr. Woodcock what she needs today, and keep her updated? Thank you.

Billy

From: Nelson, Robert "Skip"
To: Woodcock, Janet
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)
Date: Monday, September 19, 2016 8:51:57 AM
Attachments: FINAL 4045-301 Protocol amendment 3_07Jun2016.pdf

Janet,

In looking at the latest records in DARRTS for NDA 206488, it does appear that the PMC for exon 45 and 53 is described as (b) (4), and notes that the use of a placebo control may not be feasible (and, if so, recommends the use of an untreated concurrent control). However, the protocol submitted to INDs 118086 (exon 45) and 119982 (exon 53) is a double-blinded placebo-controlled (b) (4) (<https://www.clinicaltrials.gov/ct2/show/NCT02500381>). As currently written, placebo will be administered as an IV infusion once a week for up to 96 weeks. I also see that the PMR for skipping exon 51 suggests a (b) (4) study. A (b) (4) study in which all patients would receive active product (b) (4) does not raise the same ethical concerns as the infusion of a placebo for almost two years. If FDA believes that a (b) (4) study would be informative (which it would be if a difference was noted), (b) (4)

(b) (4)
(b) (4)
(b) (4)

An IR to clarify the Sponsor's intentions would be useful.

Again, happy to discuss further.

Skip Nelson

Deputy Director and Senior Pediatric Ethicist

Office of Pediatric Therapeutics, FDA

Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Woodcock, Janet
Sent: Friday, September 16, 2016 6:37 PM
To: Nelson, Robert 'Skip'
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

They are not using the (b) (4). It is a postmarket commitment per the approval letter, but much of the protocol is to be developed. My understanding is that they are (b) (4)

.jw

From: Nelson, Robert 'Skip'
Sent: Friday, September 16, 2016 10:57 AM
To: Woodcock, Janet
Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)
Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter

Study of SRP-4045 and SRP-4053 in Patients With DMD)

I will double-check, but my understanding is that the trial is a double-blinded (b) (4) using a placebo infusion (thus raising the issue about central line access for a two year trial). An open label trial with a concurrent no treatment control would not raise the same ethical concerns (but may be uninformative given the use of the (b) (4)).

Skip Nelson

Deputy Director and Senior Pediatric Ethicist

Office of Pediatric Therapeutics, FDA

Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Woodcock, Janet

Sent: Friday, September 16, 2016 10:41 AM

To: Nelson, Robert 'Skip'

Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)

Subject: RE: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

My understanding of the current protocol is that is a randomized (b) (4) controlled study in which the control arm is not treated, at least in the US. jw

From: Nelson, Robert 'Skip'

Sent: Friday, September 16, 2016 10:22 AM

To: Woodcock, Janet

Cc: Dunn, Billy; Bastings, Eric; Temple, Robert; Unger, Ellis; Choy, Fannie (Yuet)

Subject: FW: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

Importance: High

Dear Janet,

DNP suggested I forward my concerns (detailed below) to you as you are leading the review of this application. My recommendation is to send an IR to the Sponsor asking about the IRB review of the planned ESSENCE trial. I appreciate the sensitivity of this recommendation given the issues surrounding the review of this product. Please let me know if I can answer any questions you may have about this recommendation. Thank you for your attention to this request.

Skip Nelson

Deputy Director and Senior Pediatric Ethicist

Office of Pediatric Therapeutics, FDA

Office: WO32-5152; Tele: (301) 796-8665; E-mail: Robert.Nelson@fda.hhs.gov

From: Nelson, Robert 'Skip'

Sent: Thursday, August 18, 2016 3:20 PM

To: Farkas, Ronald; Bastings, Eric

Cc: Dunn, Billy; Choy, Fannie (Yuet)

Subject: ESSENCE Confirmatory study, 4045-301 (A Double-Blind, Placebo-Controlled, Multicenter Study of SRP-4045 and SRP-4053 in Patients With DMD)

Importance: High

Dear Ron and Eric,

I am writing to express a concern about the ESSENCE trial based on our previous communication and conversations I have had with parents of boys with DMD. Although I appreciate that any communication with the sponsor, Sarepta, may be delayed until after a decision is made about the pending NDA application; however, I believe an Information Request should be sent ASAP to the sponsor asking why the ESSENCE protocol has not been referred by the (b) (4) to FDA for review under 21 CFR 50.54. Let me explain my reasoning.

- (1) On July 5, 2016, the sponsor sent the following communication: (b) (4)

(b) (4)

From this communication, I conclude that the (b) (4) thought that the use of central venous catheters in the US may be necessary, and could be justified on scientific and ethical grounds.

- (2) As you know, the use of implantable central venous catheters for the administration of placebo is not in compliance with 21 CFR 50.53 (as it presents more than a minor increase over minimal risk without the prospect of any direct benefit). As such, absent federal panel review, a local IRB in the US is unable to approve such a procedure. In addition, absent federal panel review, FDA considers such a procedure an "unreasonable risk." Our regulations, however, have a process under 21 CFR 50.54 by which these procedures can be reviewed by a federal panel and approved, if appropriate, by the FDA Commissioner (in essence, determining that the risk is "reasonable" given the context). An IRB may refer a protocol for federal panel review if "the IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." I can only assume, based on the Sponsor's characterization of the (b) (4) assessment, that this criterion for referral has been met. The US is the only country I know of that has this regulatory framework limiting the authority of local IRBs with respect to approving these procedures, so I am not surprised by the different decisions being made in the EU.
- (3) Parents of boys with DMD appreciate the likelihood that many if not most of the DMD boys will require central venous access to be able to tolerate weekly infusions for the length of this study (nearly two years). Questions have been raised (to me in conversation) as to whether the decision not to refer the study for federal panel review under 21 CFR 50.54 is a back-handed way to assure that the clinical trial is not feasible in the US. At the very least, it would place these DMD boys at risk without the potential compensating benefit of a sufficiently long course of the investigational product to be able to see a meaningful clinical

benefit. I consider this a serious ethical issue that FDA should not even implicitly endorse by failing to send an IR.

Given these concerns, I strongly recommend that FDA send an IR to the sponsor, Sarepta, asking why the [REDACTED] (b)(4) has not referred the protocol for review under 21 CFR 50.54 given their assessment of the protocol. I will not speculate on what recommendation(s) might emerge from such a review, which is conducted by the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, as I am the person responsible for coordinating the AC meeting. However, I consider it a serious ethical breach of the responsibility of the [REDACTED] (b)(4) (and perhaps other reviewing IRBs) to make a finding that merits referral under 21 CFR 50.54 and yet not make that referral.

Let me know if I can answer any questions.

Skip

Robert "Skip" Nelson, MD PhD
Deputy Director and Senior Pediatric Ethicist, Office of Pediatric Therapeutics, FDA
Tele: (301) 796-8665; Mobile: (240) 328-7146; Fax: (301) 847-8619
E-mail: Robert.Nelson@fda.hhs.gov
Website: <http://www.fda.gov/pediatrics>

Mailing Address:
WO/Building 32, Room 5152
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



CLINICAL STUDY PROTOCOL

DRUG: SRP-4045 Injection and SRP-4053 Injection

STUDY NUMBER: 4045-301

STUDY TITLE: A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy

IND NUMBER: 118,086 (SRP-4045)
119,982 (SRP-4053)

EUDRACT NUMBER: 2015-002069-52

SPONSOR: Sarepta Therapeutics, Inc.
215 First Street
Cambridge, MA 02142 USA
Phone: +1-617-274-4000

CURRENT VERSION DATE: (b) (4)

REPLACES VERSION DATE: (b) (4)

CONFIDENTIALITY STATEMENT

The information contained in this document, is the property of the Sponsor and is confidential. This information may not be disclosed, reproduced or distributed to anyone other than personnel directly involved in the conduct of the study and in response to a relevant Institutional Review Board/Independent Ethics Committee and Review by a Regulatory Authority as required by the applicable laws and regulations, without the written authorization of the Sponsor, except to the extent necessary to obtain written informed consent from those individuals to whom the drug may be administered. These restrictions will continue to apply after the study has closed.

From: [Rodriguez, Jennifer](#)
To: [Ligon, Sharnell \(CDER\)](#); [Kraus, Tom](#); [Woodcock, Janet](#); [Conover, Katie](#); [Califf, Robert](#); [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Sharp, Jeremy](#); [Throckmorton, Douglas C](#)
Cc: [Rawlings, Kimberly](#); [Young, Jason](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: FOR TEAM REVIEW: Tentative Timeline
Date: Friday, September 16, 2016 4:17:29 PM
Attachments: [NDA206488_eteplirsen_FDAApprovedLabelingText091616.pdf](#)
[image001.png](#)

Adding Deborah, who is reviewing the comms against this information.

From: Ligon, Sharnell (CDER)
Sent: Friday, September 16, 2016 3:39 PM
To: Kraus, Tom; Woodcock, Janet; Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Sharp, Jeremy; Throckmorton, Douglas C
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: RE: FOR TEAM REVIEW: Tentative Timeline
Importance: High

Good Afternoon,

Per your request, attached is the final labeling for eteplirsen.

Kind Regards,

Sharnell

From: Kraus, Tom
Sent: Friday, September 16, 2016 12:02 PM
To: Woodcock, Janet; Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Sharp, Jeremy; Throckmorton, Douglas C; Ligon, Sharnell (CDER)
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: RE: FOR TEAM REVIEW: Tentative Timeline

Janet, We should get you the final memo shortly. In the meantime, please send OCC the final labeling so they can conform the comms.

From: Woodcock, Janet
Sent: Friday, September 16, 2016 10:48 AM
To: Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Sharp, Jeremy; Throckmorton, Douglas C; Ligon, Sharnell (CDER)
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: RE: FOR TEAM REVIEW: Tentative Timeline

I won't be here Monday, Doug Throckmorton is acting and aware of the plan, The letter can get pput itno DAARTS on Monday AM. jw

From: Conover, Katie
Sent: Friday, September 16, 2016 9:56 AM
To: Woodcock, Janet; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Sharp, Jeremy
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason

Subject: FOR TEAM REVIEW: Tentative Timeline

Hello all --

Here is a timeline for Monday morning. Let us know if it looks good to you.

Also – if we could take a look at the CDER All Hands (as that will most likely also be viewed externally) – that would be great.

Tentative Timeline:

Note: Jen will coordinate, giving each group the greenlight to proceed, in order to ensure adherence to the timeline below.

-
9:00 – Janet signs approval; alerts company; company confirms receipt

Following timeline dependent on company receipt confirmation

9:15 – Janet sends confirmation email of company receipt to: Robert Califf, Rachel Sherman, Tom Kraus, Jeremy Sharp, Liz Dickenson, Katie Conover, Jennifer Rodriguez, Dayle Cristinzio

- OL/OB conducts close hold calls

9:30 – FDA issues Press release; letter, label and memos post to website; and CDER issues all hands email

Following press release:

- OL/OB additional email outreach
- OHCA stakeholder outreach
- Standard social media amplification

Thank you!

Katie and team

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)

- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 35\%$ and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	11	DESCRIPTION
2	DOSAGE AND ADMINISTRATION	12	CLINICAL PHARMACOLOGY
2.1	Dosing Information	12.1	Mechanism of Action
2.2	Preparation Instructions	12.2	Pharmacodynamics
2.3	Administration Instructions	12.3	Pharmacokinetics
3	DOSAGE FORMS AND STRENGTHS	13	NONCLINICAL TOXICOLOGY
4	CONTRAINDICATIONS	13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
6	ADVERSE REACTIONS	14	CLINICAL STUDIES
6.1	Clinical Trials Experience	16	HOW SUPPLIED/STORAGE AND HANDLING
8	USE IN SPECIFIC POPULATIONS	16.1	How Supplied
8.1	Pregnancy	16.2	Storage and Handling
8.2	Lactation		
8.4	Pediatric Use		
8.5	Geriatric Use		
8.6	Patients with Renal or Hepatic Impairment		
10	OVERDOSAGE		

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

- a. Calculate the total dose of EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.
- b. Allow vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.
- c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.
- d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.
- e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.
- f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6

patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week [see *Clinical Studies (14)*].

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended [see *Dosage and Administration (2.1)*].

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week¹ EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8)	Placebo (N=4)
	%	%
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

¹ 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥ 30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in $\geq 10\%$ of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated 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, including pediatric patients [see *Clinical Studies (14)*].

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

There is no experience with overdose of EXONDYS 51.

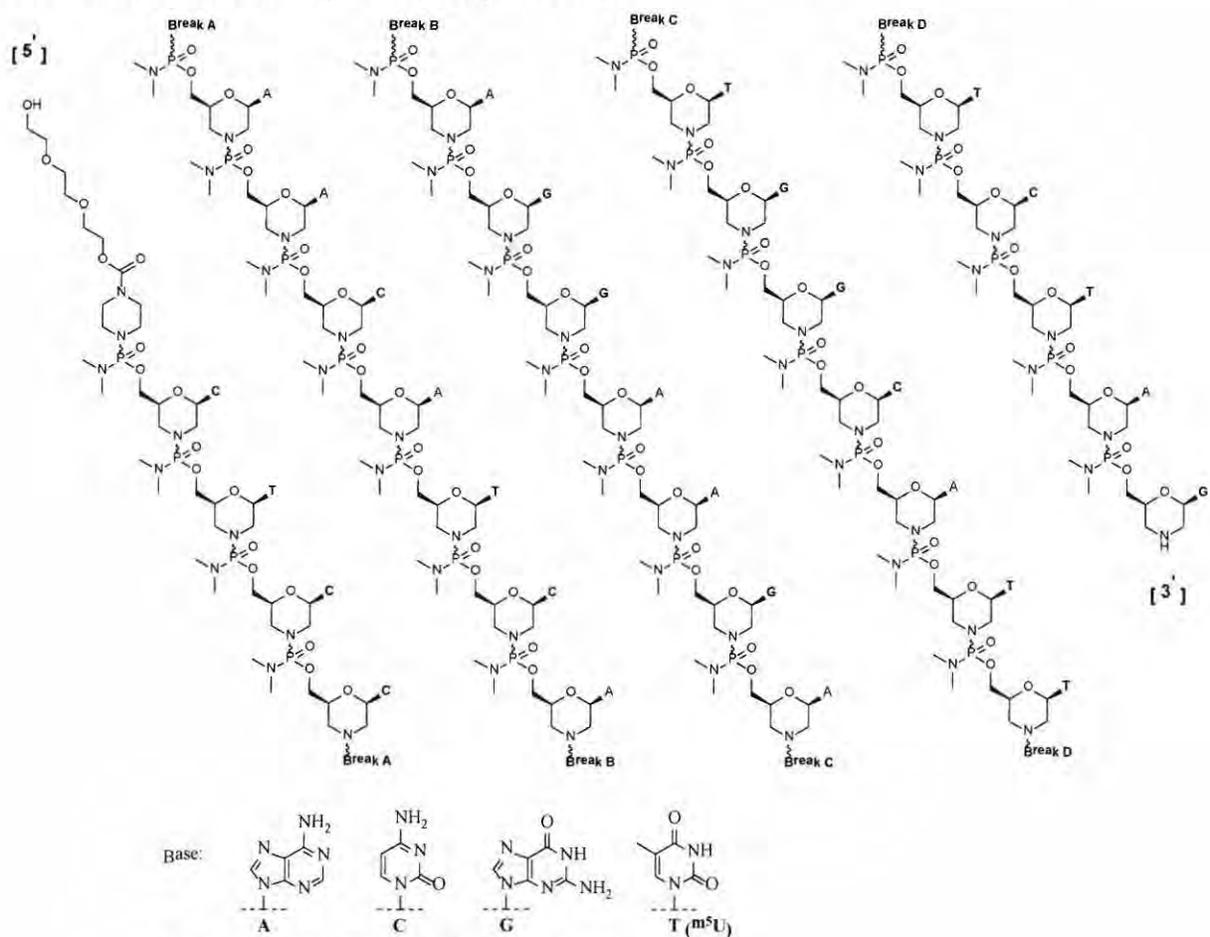
11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 0.2 mg potassium chloride, 0.2 mg potassium phosphate monobasic, 8 mg sodium chloride, and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [see *Clinical studies (14)*].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 [see *Clinical studies (14)*]. The median increase in truncated dystrophin in Study 3 was 0.1% [see *Clinical Studies (14)*].

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (V_{ss}) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max} . Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC)

in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was $0.16\% \pm 0.12\%$ (mean \pm standard deviation) of the dystrophin level in a healthy subject and $0.44\% \pm 0.43\%$ after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin

1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; $p=0.008$

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

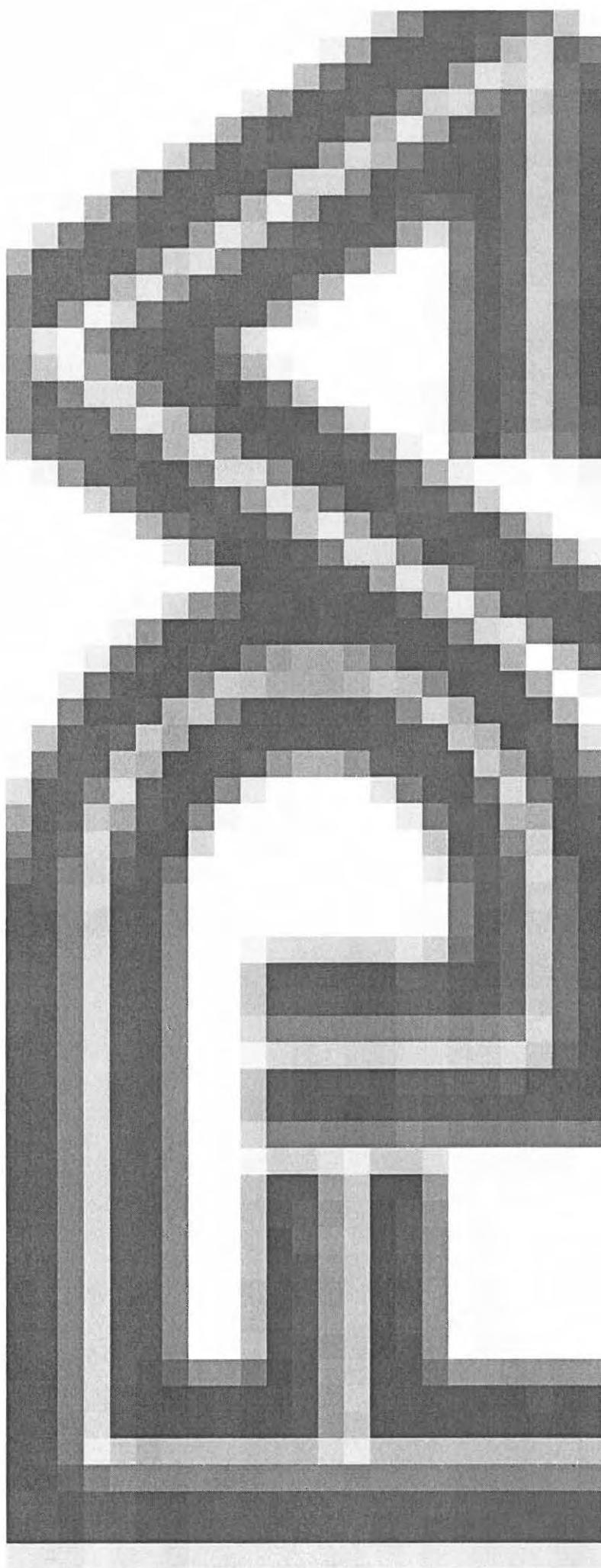
EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA



From: [Rodriguez, Jennifer](#)
To: [Throckmorton, Douglas C](#); [Kraus, Tom](#); [Woodcock, Janet](#); [Conover, Katie](#); [Califf, Robert](#); [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Sharp, Jeremy](#); [Ligon, Sharnell \(CDER\)](#)
Cc: [Rawlings, Kimberly](#); [Young, Jason](#)
Subject: RE: FOR TEAM REVIEW: Tentative Timeline
Date: Friday, September 16, 2016 3:27:53 PM
Attachments: [image001.png](#)

Thank you, all. It seems that we are all OK with the below timeline. If we don't get any further input by 3:45pm today, I will share this timeline with the key OL, OB and OHCA contacts so they can plan accordingly.

Final comms will be shared at a later point, following final OCC review in advance of Monday.

From: Throckmorton, Douglas C
Sent: Friday, September 16, 2016 12:34 PM
To: Kraus, Tom; Woodcock, Janet; Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Sharp, Jeremy; Ligon, Sharnell (CDER)
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: Re: FOR TEAM REVIEW: Tentative Timeline

Thanks

Douglas C Throckmorton MD
Deputy Director for Regulatory Programs
CDER FDA
301-796-5400

From: Kraus, Tom
Sent: Friday, September 16, 2016 12:02 PM
To: Woodcock, Janet; Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Sharp, Jeremy; Throckmorton, Douglas C; Ligon, Sharnell (CDER)
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: RE: FOR TEAM REVIEW: Tentative Timeline

Janet, We should get you the final memo shortly. In the meantime, please send OCC the final labeling so they can conform the comms.

From: Woodcock, Janet
Sent: Friday, September 16, 2016 10:48 AM
To: Conover, Katie; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Sharp, Jeremy; Throckmorton, Douglas C; Ligon, Sharnell (CDER)
Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: RE: FOR TEAM REVIEW: Tentative Timeline

I won't be here Monday, Doug Throckmorton is acting and aware of the plan, The letter can get pput itno DAARTS on Monday AM. jw

From: Conover, Katie
Sent: Friday, September 16, 2016 9:56 AM
To: Woodcock, Janet; Califf, Robert; Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Sharp, Jeremy

Cc: Rodriguez, Jennifer; Rawlings, Kimberly; Young, Jason
Subject: FOR TEAM REVIEW: Tentative Timeline

Hello all --

Here is a timeline for Monday morning. Let us know if it looks good to you.

Also – if we could take a look at the CDER All Hands (as that will most likely also be viewed externally) – that would be great.

Tentative Timeline:

Note: Jen will coordinate, giving each group the greenlight to proceed, in order to ensure adherence to the timeline below.

9:00 – Janet signs approval; alerts company; company confirms receipt

Following timeline dependent on company receipt confirmation

9:15 – Janet sends confirmation email of company receipt to: Robert Califf, Rachel Sherman, Tom Kraus, Jeremy Sharp, Liz Dickenson, Katie Conover, Jennifer Rodriguez, Dayle Cristinzio

- OL/OB conducts close hold calls

9:30 – FDA issues Press release; letter, label and memos post to website; and CDER issues all hands email

Following press release:

- OL/OB additional email outreach
- OHCA stakeholder outreach
- Standard social media amplification

Thank you!

Katie and team

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: IHC baseline differences
Date: Friday, September 16, 2016 2:54:46 PM

I spoke with Ash again and we confirmed that images were prepared differently for analysis between the images used for week 48 and those for week 180, starting of course with new stains prepared concurrently with the staining for the new wk 180 biopsies but also several other steps that would expectedly have conservatively reduced the number of positive staining cells both in baseline and wk 180 samples. Again, no surprise in the different baseline numbers. Also confirmed that bioquant for wk 180 was done correctly in assessing randomly selected images from baseline and similarly from wk 180 for the relevant subject and the entire field was used but focused on the fiber images. This would be the correct way to do this and it was also positive achieving a fluorescent intensity value of about half of Beckers patients in the same analysis. Rich.

From: [Choy, Fannie \(Yuet\)](#)
To: [Woodcock, Janet](#)
Cc: [Yasuda, Sally](#); [Dunn, Billy](#); [Unger, Ellis](#); [Bastings, Eric](#); [Kozauer, Nicholas](#); [Ware, Jacqueline H](#); [Hughes, Alice](#); [Choy, Fannie \(Yuet\)](#)
Subject: RE: Sarepta approval letter
Date: Friday, September 16, 2016 2:35:56 PM
Attachments: [NDA206488_FINAL_AccApproval_Ltr & labeling_091615.pdf](#)
[NDA206488_FINAL_AccApproval_091615.doc](#)

Dr. Woodcock,

We have received agreement from Sarepta to adjust the milestone dates for the PMRs/PMCs earlier today. The letter has been revised with the new dates. Labeling was agreed upon on 8/3/16.

Attached please find the approval letter for NDA 206488 / eteplirsen. The PDF file is the final version of the letter with content of labeling attached. This PDF is the version that we'd upload in DARRTS for sign-off. I have also included a Word version of the letter in case you have further edits, please let me know. Billy mentioned in the earlier email that you're planning to sign in hard copy today. Will you be signing the attached PDF version?

Thanks
Fannie

From: Woodcock, Janet
Sent: Friday, September 16, 2016 10:45 AM
To: Yasuda, Sally; Dunn, Billy; Unger, Ellis; Bastings, Eric; Choy, Fannie (Yuet); Kozauer, Nicholas; Hughes, Alice; Ware, Jacqueline H
Subject: RE: Sarepta approval letter

Sounds right. jw

From: Yasuda, Sally
Sent: Friday, September 16, 2016 9:33 AM
To: Dunn, Billy; Unger, Ellis; Bastings, Eric; Choy, Fannie (Yuet); Kozauer, Nicholas; Hughes, Alice; Ware, Jacqueline H
Cc: Woodcock, Janet
Subject: RE: Sarepta approval letter

We should push back the milestone dates by 2 months for the PMRs and PMCs.

There is required template language in the approval letter that acknowledges the milestone dates sent by the company. Can we send them revised dates this morning and ask for their agreement by this morning? We need those dates in the PMR/PMC templates and in the approval letter.

Thank you,

Sally Jo

From: Dunn, Billy
Sent: Friday, September 16, 2016 9:19 AM
To: Unger, Ellis; Bastings, Eric; Choy, Fannie (Yuet); Kozauer, Nicholas; Yasuda, Sally; Hughes, Alice; Ware, Jacqueline H
Cc: Woodcock, Janet
Subject: Sarepta approval letter

Folks,

Dr. Woodcock contacted me this morning interested in moving forward with signing the approval letter in hard copy today. She is copied on this email. Could folks, consulting with Ellis, work on getting Dr. Woodcock what she needs today, and keep her updated? Thank you.

Billy

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 206488
Communication Type:	Correspondence
Communication Group:	NDA Action
Communication Name:	Accelerated Approval
Communication ID:	COR-NDAACTION-04
Drafted by:	Choy, Kelley, Ware 9/16/16
Clearance History:	M Chelliah / Heimann (CMC) 6/24/16, 6/30/16; Yasuda/Hughes 6/28/16, Yasuda 7/20/16, 8/8/16, 9/16/16; SRT 6/30/16, 7/18/16, 7/19/16; Locicero 7/1/16; Bastings 7/1/16, 9/16/16; J Woodcock
Finalized:	
Filename:	
Signatory Authority:	NMEs and 351(a) BLAs must be signed by the Office Director or Deputy Office Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use when approving an NDA under 21 CFR 314.510 (approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity).
Notes:	

Version: 02/11/2016

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA 206488

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We acknowledge receipt of your major amendment dated January 8, 2016, which extended the goal date by three months.

This new drug application provides for the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 206488.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, we refer to your June 10, 2016, submission in which you commit to implement the carton container label revisions requested in our June 6, 2016, correspondence. Specifically, you agree to remove the reference to the compendial grades from the carton labels at the time of next printing, but no later than 120 days post-approval, and to notify us of this change via submission of a “Changes Being Effectuated” supplemental application.

PRODUCT QUALITY

Based on evaluation of the stability data provided, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°C).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number: PRV NDA 206488. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of

times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2016. This requirement, along with required completion dates as agreed upon on September 16, 2016, is listed below.

- 3095-1 In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Draft Protocol Submission: 10/2016
Final Protocol Submission: 04/2017
Trial Completion: 11/2020
Final Report Submission: 05/2021

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocol to your IND 077429 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity or an unexpected serious risk of immunogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3095-2 A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2016
Final Protocol Submission:	03/2017
Study Completion:	04/2020
Final Report Submission:	06/2020

- 3095-3 A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2016
Final Protocol Submission: 01/2017
Study Completion: 05/2018
Final Report Submission: 06/2018

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies.

- 3095-4 A study to evaluate:
1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
 2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2017
Final Protocol Submission: 08/2017
Study Completion: 12/2017
Final Report Submission: 02/2018

Additional guidance for immunogenicity assay development, though more specific for therapeutic protein products, may be found in the draft guidance: "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products"

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocols prior to initiation of the studies.

Submit the protocols to your IND 077429, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-5 Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2016
Final Protocol Submission: 04/2017
Trial Completion: 04/2021
Final Report Submission: 10/2021

A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-6 Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

- 3095-7 Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) results that were observed at lot release.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

Submit clinical protocols to your IND 077429 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic

License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

From: [Dunn, Billy](#)
To: [Woodcock, Janet](#)
Subject: Re: Sarepta
Date: Friday, September 16, 2016 9:15:22 AM

I'm not sure what you and Ellis have worked out regarding signing, but the team has been preparing the letter and it should be ready to go or nearly so. I will send a separate email to the team with you copied.

Billy

From: Woodcock, Janet
Sent: Friday, September 16, 2016 8:56 AM
To: Dunn, Billy
Subject: Sarepta

Is the approval letter prepared? I assume I am going to sign it. I'll be out Monday, so maybe I can get and sign a hardcopy today and the letter can be e-signed Monday and entered into DAARTS. TX
jw

From: [Rice, Crystal](#)
To: [Woodcock, Janet](#)
Subject: RE: Draft CD note, eteplirsen -- for your current review
Date: Friday, September 16, 2016 9:48:16 AM

Okay, sure, that's fine. I'm here all day. I'm on leave Monday, but Michelle Meadows will be available to take over. -- Thank you! -- Crystal

From: Woodcock, Janet
Sent: Friday, September 16, 2016 8:57 AM
To: Rice, Crystal
Subject: RE: Draft CD note, eteplirsen -- for your current review

Let me look at it. I don't concur with the suggestions, for technical reasons. jw

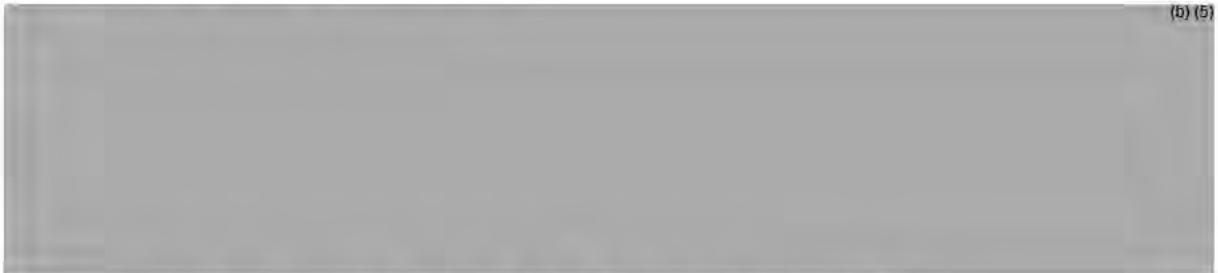
From: Rice, Crystal
Sent: Thursday, September 15, 2016 3:28 PM
To: Woodcock, Janet
Cc: Shreeve, Chris; Rice, Crystal
Subject: Draft CD note, eteplirsen -- for your current review

Hi Dr. Woodcock,

To bring current, attached you'll find the Center Director note for eteplirsen that you reviewed and cleared in early August. Since it has been more than a month since you've reviewed, would you like to take another look?

Our strategic communications lead took another look this morning, following her review of the current communications materials.

She suggested two tweaks for consideration:



Do you concur with these suggested changes? Do you have any other changes?

Thank you.
Crystal

Email subject line: **Approval of first drug for Duchenne muscular dystrophy**

CDER Staff:

Today, FDA approved the first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children. The drug,

Exondys 51 (eteplirsen) injection, is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Exondys 51 was approved under the accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy. Accelerated approval is based on data that shows the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement.

While accelerated approval provides earlier patient access to promising new drugs, under its provisions FDA requires the sponsor to conduct clinical trials to verify the predicted clinical benefit of the drug. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to show that the drug improves motor function.

The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework. In this case, flexibility is warranted because of 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 life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway.

In June 2015, FDA issued a [draft guidance](#) for industry on developing drugs for the treatment of DMD and related dystrophinopathies – one year following our receipt of a proposed draft guidance for consideration from the advocacy group, Parent Project Muscular Dystrophy (PPMD). This effort highlights how collaboration between engaged stakeholders and FDA can contribute to drug development. We appreciate PPMD's tireless efforts, and value their and the DMD community's input.

FDA held an [advisory committee meeting](#) on April 25, 2016 to discuss the marketing application for this drug. The advisory committee recommended that there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. The AC also voted 7-6 against accelerated approval, because of uncertainties about the dystrophin data presented by the sponsor. Subsequently, the sponsor submitted additional data showing evidence of dystrophin production.

I would like to acknowledge the work done by the review team. The effort spent to evaluate the application data and scientific discussions are much appreciated.

We will continue to work with sponsors to facilitate the development and approval of effective treatments for DMD and other rare diseases.

For more information about DMD, and today's approval, visit (*Press release URL pending*).

Janet Woodcock

Crystal Rice
Internal Communications Program
Division of Health Communications
Office of Communications
U.S. FDA's Center for Drug Evaluation and Research
10001 New Hampshire Avenue, Rm 417B
Silver Spring, MD 20993
301-796-3111 Crystal.Rice@fda.hhs.gov

From: Sipes, Grail
To: Woodcock, Janet
Subject: Re: Follow up on Eteplirsen
Date: Thursday, September 15, 2016 10:20:40 PM

That's funny - I was out with a bunch of people for Bruce Kuhlik's departure and Tom was telling me he had to go make a call to you. I wondered whether it might be this!

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 7:07 PM
To: Sipes, Grail
Subject: Re: Follow up on Eteplirsen

Sounds like not, just heard from Tom k. Jw

From: Sipes, Grail <Grail.Sipes@fda.hhs.gov>
Date: September 15, 2016 at 5:48:36 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: Re: Follow up on Eteplirsen

Just heard from Liz that approval may be tomorrow after all. Stay tuned....

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 4:43 PM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

Tx very much for the update. Did not know. Jw

From: Sipes, Grail <Grail.Sipes@fda.hhs.gov>
Date: September 15, 2016 at 4:30:28 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: RE: Follow up on Eteplirsen

Update:

- DIDP (Nancy S and Howard Phillips) have finished redacting all 5 documents listed below, except RMC's, which should be finalized tomorrow. Nancy estimates she would just need a few hours more to redact the RMC memo and check everything against the final approved labeling.
- Liz believes approval will be Monday. I'm not sure who is controlling the timing of approval, but redaction is not the holdup.

You may know all this already, but just in case!

Thx Grail

From: Woodcock, Janet
Sent: Wednesday, September 14, 2016 6:00 PM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

Ok thanks for all your competence on this!! And Nancy's!! jw

From: Sipes, Grail
Sent: Wednesday, September 14, 2016 5:54 PM
To: Woodcock, Janet
Subject: RE: Follow up on Eteplirsen

Hi Janet,

An update: I talked to Liz and Nancy Sager. Everything is in a good place (largely thanks to Nancy Sager's being completely on top of everything, as usual!).

The three of us were in basic agreement about the documents that should be made available as close in time as possible to the announcement of the approval. They are as follows, and Nancy believes she can have these all redacted by Friday:

- ODE Director decisional memo (Ellis Unger), 43 pages
- CD decisional memo (your memo)
- Ellis Unger appeal memo
- Acting Chief Scientist memo
- RMC decisional memo (this is the only one of this group that is not yet finalized – Liz believes he is seeking final comments today from CDER)

I think this set of documents lines up with what you had in mind, but please let me know if I am wrong. Liz, Nancy and I are all comfortable that together, they meet the "summary review" requirement. The plan would be to post all of them at the "summary review" link on the page with the approval (at the time of approval), since all of them relate to the dispute and how it was resolved.

Liz believes approval may happen either this Friday (9/16) or this coming Monday (9/19).

If you have any questions, just let me know!

Thx, Grail

From: Woodcock, Janet

Sent: Wednesday, September 14, 2016 7:44 AM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

That would be great, thanks. jw

From: Sipes, Grail
Sent: Tuesday, September 13, 2016 10:16 PM
To: Woodcock, Janet
Subject: Re: Follow up on Eteplirsen

Yes. It was in FDAAA. But a few years ago (late 2013) DIDP came to CDER management with a recommendation on how to implement. I can explain more tomorrow during our 1:1 in the afternoon -- would that work? If not, just let me know and we can touch base earlier.

Thx Grail

From: Woodcock, Janet
Sent: Tuesday, September 13, 2016 5:28 PM
To: Sipes, Grail
Subject: Fwd: Follow up on Eteplirsen

Do you know what kind of statutory requirement this is? Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 13, 2016 at 3:57:39 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out

on the schedule.

Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: RE: New memo
Date: Thursday, September 15, 2016 5:32:21 PM

I called and left a message for Ash. Rich.

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 5:20 PM
To: Moscicki, Richard
Subject: RE: New memo

You can ask Ash. I ran into him today, told him you might call. Jw

From: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>
Date: September 15, 2016 at 5:05:02 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: RE: New memo

I think they also changed the analysis for intensity. Originally they only looked at the intensity of positive fibers compared to background, but we suggested looking at the whole field which I thought they then did and still got a positive result. Rich.

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 4:27 PM
To: Moscicki, Richard
Subject: Re: New memo

This is how I remember it too and I put some of that in my memo as Ash told me the change in methods. That was for the percent positive fibers. The intensity analysis was done the same as far as technique. Jw

From: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>
Date: September 15, 2016 at 4:13:47 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: New memo

Hi Janet, I looked at the email from Ellis, I don't quite get it as that information was available. It seems strange that he is only now recognizing this. I reviewed the same information and so did Ash when we all discussed the information and I believe that you too were aware of it. We understand that the methods for analyzing the immunohistochemistry and the rules for positive and negative fibers were different in the different analyses that he is referring to in the IHC and that explained

the difference in how baselines were counted. The important thing is that irrespective of the method and the consequent baseline there was a substantial increase in positive fibers in subsequent biopsies. The finding was also consistent with the method employed later to analyze immunofluorescent intensity. The data does not negate the Western blots which you used primarily to make your decision. Your use of the literature told you that even small amounts of dystrophin might make a difference, I don't think you were trying to say that the numbers were directly comparable from study to study. I can go back to the data and make sure the specific numbers he is talking about are how I am remembering it. Rich.

From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: RE: memo
Date: Thursday, September 15, 2016 5:31:33 PM

So I checked and indeed you mentioned the discrepancy in your memorandum so you were very aware and understood the reason for it. The Bioquant assay report for the 180 day samples is where I thought the target (entire field vs just positive fibers) had changed but could not verify that in the report when I looked it up. Nevertheless it also showed a positive change.

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 7:20 AM
To: Moscicki, Richard
Subject: Fwd: memo

Can you figure out what Ellis is talking about here? Re the IHC data! His memo is in DARRTS. Feel free to talk to Ash. I think I had already figured this out myself. Jw

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Date: September 14, 2016 at 6:51:46 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Borio, Luciana <Luciana.Borio@fda.hhs.gov>
Subject: RE: memo

Rob,

I have concerns with respect to two areas of your memo, first, whether proper procedures were followed such that all evidence and analyses were reviewed by the Center Director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the Center Director, as was clearly the case here. I've also returned your memo with just a few tracked comments and text.

1. Whether proper procedures were followed; whether all evidence was considered

Having read your draft memo and the August 8, 2016, memorandum of the Scientific Dispute Process Review Board (SDR Board), I do not agree with your conclusions that:

- all applicable processes and procedures were followed;
- the appealing parties had ample opportunity to present their views; and
- the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

As Director of Office of Drug Evaluation-I, I provide a final level of review and sign-off for various New Drug Applications. Not infrequently, as I write these memoranda, I recognize areas where there is lack of clarity, or I may have concerns about the data or the reviews. In these situations, I find myself doing some last minute "digging" on my own.

Such was the case here. As I was writing my Complete Response memorandum for eteplirsen, I began to recognize the very confusing nature of the immunohistochemistry results from Study 201/202. As stated in the SDR Board's memo (page 12), Dr. Woodcock "...thought that the review team's presentation of the IHC data, in particular, was confusing."

In trying to understand the ambiguities and discrepancies myself, I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers. (All slides had been analyzed by the same panel of pathologists.) As noted in Figure 2 of my appeal, for the 3 patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, Advisory Committee meeting.

Because of this lack of reliability, there is simply no way to relate or compare the applicant's immunohistochemistry results to results from other laboratories reported in the literature.

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): "Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014," and page 20: "...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level."

It follows, therefore, that:

- All applicable processes and procedures were not followed;
- I did not have the opportunity to present this highly relevant scientific evidence to Dr. Woodcock; and
- Dr. Woodcock's decision to grant accelerated approval was made prior to consideration of all relevant scientific evidence.

The information showing the applicant's lack of ability to reproduce its own dystrophin results is critically important because any attempt to identify a quantity of truncated dystrophin that is "reasonably likely to predict clinical benefit" would hinge on the demonstration of a relationship between skeletal muscle dystrophin content and physical function, presumably as accepted by the scientific/medical community. With respect to the immunohistochemistry analyses in Study 201/202, the applicant's inability to reproduce its own findings raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in

the literature.

With respect to the Western blot analyses, the applicant stated at the Advisory Committee meeting that their data should not be compared to data from other laboratories (page 14 of my appeal):

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation....Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In conclusion therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is “reasonably likely to predict clinical benefit.” There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program.

Unaware of my final conclusions on this matter, Dr. Woodcock did not rebut the above reasoning. As I noted (and the SDR Board appeared to agree), she provided no cogent rationale for her decision that the barely detectable amount of dystrophin produced is “reasonably likely to predict clinical benefit.” Dr. Woodcock told the SDR Board that her decision was based on her 30 years of experience at FDA and her own “medical/scientific judgment.” (SDR Board Memo, page 16).

I think it will be important for the regulatory record to reflect that there was no scientific basis underlying the conclusion of “reasonably likely” in this case. This was simply a judgment call by Dr. Woodcock. (Dr. Woodcock might have also taken the position that, in this desperate patient population, *any* dystrophin production would suffice as a basis for accelerated approval, but she didn’t state this.)

2. Whether this decision will set a general precedent and degrade the evidence standard for accelerated approval

In your draft Commissioner’s Decisional Memorandum, I fail to see any explicit basis for considering how DMD differs from many other rare diseases, i.e., why DMD/eteplirsen represents a “unique situation that will not set a general precedent for the standard of evidence supporting drug approvals under the accelerated approval pathway.” You note that “...the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.”

We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann–Pick disease, Pelizaeus–Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy. Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn’t apply for these diseases.

Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a

surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for these disorders. But in my opinion, this approach should receive broader public (and FDA) input before being implemented.

Your decision seems to say that the “reasonably likely” standard for accelerated approval need have no quantitative component at all. We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the “reasonably likely” test.

I thank you for your consideration in all of this.

Ellis

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board’s memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there

is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: RE: New memo
Date: Thursday, September 15, 2016 5:05:02 PM

I think they also changed the analysis for intensity. Originally they only looked at the intensity of positive fibers compared to background, but we suggested looking at the whole field which I thought they then did and still got a positive result. Rich.

From: Woodcock, Janet
Sent: Thursday, September 15, 2016 4:27 PM
To: Moscicki, Richard
Subject: Re: New memo

This is how I remember it too and I put some of that in my memo as Ash told me the change in methods. That was for the percent positive fibers. The intensity analysis was done the same as far as technique. Jw

From: Moscicki, Richard <Richard.Moscicki@fda.hhs.gov>
Date: September 15, 2016 at 4:13:47 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: New memo

Hi Janet, I looked at the email from Ellis, I don't quite get it as that information was available. It seems strange that he is only now recognizing this. I reviewed the same information and so did Ash when we all discussed the information and I believe that you too were aware of it. We understand that the methods for analyzing the immunohistochemistry and the rules for positive and negative fibers were different in the different analyses that he is referring to in the IHC and that explained the difference in how baselines were counted. The important thing is that irrespective of the method and the consequent baseline there was a substantial increase in positive fibers in subsequent biopsies. The finding was also consistent with the method employed later to analyze immunofluorescent intensity. The data does not negate the Western blots which you used primarily to make your decision. Your use of the literature told you that even small amounts of dystrophin might make a difference, I don't think you were trying to say that the numbers were directly comparable from study to study. I can go back to the data and make sure the specific numbers he is talking about are how I am remembering it. Rich.

From: [Sipes, Grail](#)
To: [Woodcock, Janet](#)
Subject: RE: Follow up on Eteplirsen
Date: Thursday, September 15, 2016 4:30:28 PM

Update:

- DIDP (Nancy S and Howard Phillips) have finished redacting all 5 documents listed below, except RMC's, which should be finalized tomorrow. Nancy estimates she would just need a few hours more to redact the RMC memo and check everything against the final approved labeling.
- Liz believes approval will be Monday. I'm not sure who is controlling the timing of approval, but redaction is not the holdup.

You may know all this already, but just in case!

Thx Grail

From: Woodcock, Janet
Sent: Wednesday, September 14, 2016 6:00 PM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

Ok thanks for all your competence on this!! And Nancy's!! jw

From: Sipes, Grail
Sent: Wednesday, September 14, 2016 5:54 PM
To: Woodcock, Janet
Subject: RE: Follow up on Eteplirsen

Hi Janet,

An update: I talked to Liz and Nancy Sager. Everything is in a good place (largely thanks to Nancy Sager's being completely on top of everything, as usual!).

The three of us were in basic agreement about the documents that should be made available as close in time as possible to the announcement of the approval. They are as follows, and Nancy believes she can have these all redacted by Friday:

- ODE Director decisional memo (Ellis Unger), 43 pages
- CD decisional memo (your memo)
- Ellis Unger appeal memo
- Acting Chief Scientist memo
- RMC decisional memo (this is the only one of this group that is not yet finalized – Liz believes he is seeking final comments today from CDER)

I think this set of documents lines up with what you had in mind, but please let me know if I am wrong. Liz, Nancy and I are all comfortable that together, they meet the "summary review"

requirement. The plan would be to post all of them at the "summary review" link on the page with the approval (at the time of approval), since all of them relate to the dispute and how it was resolved.

Liz believes approval may happen either this Friday (9/16) or this coming Monday (9/19).

If you have any questions, just let me know!

Thx, Grail

From: Woodcock, Janet
Sent: Wednesday, September 14, 2016 7:44 AM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

That would be great, thanks. jw

From: Sipes, Grail
Sent: Tuesday, September 13, 2016 10:16 PM
To: Woodcock, Janet
Subject: Re: Follow up on Eteplirsen

Yes. It was in FDAAA. But a few years ago (late 2013) DIDP came to CDER management with a recommendation on how to implement. I can explain more tomorrow during our 1:1 in the afternoon -- would that work? If not, just let me know and we can touch base earlier.

Thx Grail

From: Woodcock, Janet
Sent: Tuesday, September 13, 2016 5:28 PM
To: Sipes, Grail
Subject: Fwd: Follow up on Eteplirsen

Do you know what kind of statutory requirement this is? Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 13, 2016 at 3:57:39 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the

division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take

questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: New memo
Date: Thursday, September 15, 2016 4:13:48 PM

Hi Janet, I looked at the email from Ellis, I don't quite get it as that information was available. It seems strange that he is only now recognizing this. I reviewed the same information and so did Ash when we all discussed the information and I believe that you too were aware of it. We understand that the methods for analyzing the immunohistochemistry and the rules for positive and negative fibers were different in the different analyses that he is referring to in the IHC and that explained the difference in how baselines were counted. The important thing is that irrespective of the method and the consequent baseline there was a substantial increase in positive fibers in subsequent biopsies. The finding was also consistent with the method employed later to analyze immunofluorescent intensity. The data does not negate the Western blots which you used primarily to make your decision. Your use of the literature told you that even small amounts of dystrophin might make a difference, I don't think you were trying to say that the numbers were directly comparable from study to study. I can go back to the data and make sure the specific numbers he is talking about are how I am remembering it. Rich.

From: [Unger, Ellis](#)
To: [Califf, Robert](#)
Cc: [Woodcock, Janet](#); [Jenkins, John K](#); [Borio, Luciana](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 6:51:47 PM
Attachments: [2016 Sept 012 R2 Eteplirsen CLEAN unger.doc](#)

Rob,

I have concerns with respect to two areas of your memo, first, whether proper procedures were followed such that all evidence and analyses were reviewed by the Center Director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the Center Director, as was clearly the case here. I've also returned your memo with just a few tracked comments and text.

1. Whether proper procedures were followed; whether all evidence was considered

Having read your draft memo and the August 8, 2016, memorandum of the Scientific Dispute Process Review Board (SDR Board), I do not agree with your conclusions that:

- all applicable processes and procedures were followed;
- the appealing parties had ample opportunity to present their views; and
- the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

As Director of Office of Drug Evaluation-I, I provide a final level of review and sign-off for various New Drug Applications. Not infrequently, as I write these memoranda, I recognize areas where there is lack of clarity, or I may have concerns about the data or the reviews. In these situations, I find myself doing some last minute “digging” on my own.

Such was the case here. As I was writing my Complete Response memorandum for eteplirsen, I began to recognize the very confusing nature of the immunohistochemistry results from Study 201/202. As stated in the SDR Board’s memo (page 12), Dr. Woodcock “...thought that the review team’s presentation of the IHC data, in particular, was confusing.”

In trying to understand the ambiguities and discrepancies myself, I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers. (All slides had been analyzed by the same panel of pathologists.) As noted in Figure 2 of my appeal, for the 3 patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, Advisory Committee meeting.

Because of this lack of reliability, there is simply no way to relate or compare the applicant’s immunohistochemistry results to results from other laboratories reported in the literature.

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry

data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): “Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014,” and page 20: “...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level.”

It follows, therefore, that:

- All applicable processes and procedures were not followed;
- I did not have the opportunity to present this highly relevant scientific evidence to Dr. Woodcock; and
- Dr. Woodcock’s decision to grant accelerated approval was made prior to consideration of all relevant scientific evidence.

The information showing the applicant’s lack of ability to reproduce its own dystrophin results is critically important because any attempt to identify a quantity of truncated dystrophin that is “reasonably likely to predict clinical benefit” would hinge on the demonstration of a relationship between skeletal muscle dystrophin content and physical function, presumably as accepted by the scientific/medical community. With respect to the immunohistochemistry analyses in Study 201/202, the applicant’s inability to reproduce its own findings raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in the literature.

With respect to the Western blot analyses, the applicant stated at the Advisory Committee meeting that their data should not be compared to data from other laboratories (page 14 of my appeal):

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation...Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In conclusion therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is “reasonably likely to predict clinical benefit.” There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program.

Unaware of my final conclusions on this matter, Dr. Woodcock did not rebut the above reasoning. As I noted (and the SDR Board appeared to agree), she provided no cogent rationale for her decision that the barely detectable amount of dystrophin produced is “reasonably likely to predict clinical benefit.” Dr. Woodcock told the SDR Board that her decision was based on her 30 years of experience at FDA and her own “medical/scientific judgment.” (SDR Board Memo, page 16).

I think it will be important for the regulatory record to reflect that there was no scientific basis

underlying the conclusion of “reasonably likely” in this case. This was simply a judgment call by Dr. Woodcock. (Dr. Woodcock might have also taken the position that, in this desperate patient population, *any* dystrophin production would suffice as a basis for accelerated approval, but she didn’t state this.)

2. Whether this decision will set a general precedent and degrade the evidence standard for accelerated approval

In your draft Commissioner’s Decisional Memorandum, I fail to see any explicit basis for considering how DMD differs from many other rare diseases, i.e., why DMD/eteplirsen represents a “unique situation that will not set a general precedent for the standard of evidence supporting drug approvals under the accelerated approval pathway.” You note that “...the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.”

We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann–Pick disease, Pelizaeus–Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy. Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn’t apply for these diseases.

Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for these disorders. But in my opinion, this approach should receive broader public (and FDA) input before being implemented.

Your decision seems to say that the “reasonably likely” standard for accelerated approval need have no quantitative component at all. We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the “reasonably likely” test.

I thank you for your consideration in all of this.

Ellis

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

Scientific Dispute Regarding Approval of Sarepta Therapeutics' Eteplirsen – Commissioner's Decision

(b) (5)



10 pages of draft language have been withheld as b(5) immediately following this page

From: [Sipes, Grail](#)
To: [Woodcock, Janet](#)
Subject: RE: Follow up on Eteplirsen
Date: Wednesday, September 14, 2016 5:54:24 PM

Hi Janet,

An update: I talked to Liz and Nancy Sager. Everything is in a good place (largely thanks to Nancy Sager's being completely on top of everything, as usual!).

The three of us were in basic agreement about the documents that should be made available as close in time as possible to the announcement of the approval. They are as follows, and Nancy believes she can have these all redacted by Friday:

- ODE Director decisional memo (Ellis Unger), 43 pages
- CD decisional memo (your memo)
- Ellis Unger appeal memo
- Acting Chief Scientist memo
- RMC decisional memo (this is the only one of this group that is not yet finalized – Liz believes he is seeking final comments today from CDER)

I think this set of documents lines up with what you had in mind, but please let me know if I am wrong. Liz, Nancy and I are all comfortable that together, they meet the "summary review" requirement. The plan would be to post all of them at the "summary review" link on the page with the approval (at the time of approval), since all of them relate to the dispute and how it was resolved.

Liz believes approval may happen either this Friday (9/16) or this coming Monday (9/19).

If you have any questions, just let me know!

Thx, Grail

From: Woodcock, Janet
Sent: Wednesday, September 14, 2016 7:44 AM
To: Sipes, Grail
Subject: RE: Follow up on Eteplirsen

That would be great, thanks. jw

From: Sipes, Grail
Sent: Tuesday, September 13, 2016 10:16 PM
To: Woodcock, Janet
Subject: Re: Follow up on Eteplirsen

Yes. It was in FDAAA. But a few years ago (late 2013) DIDP came to CDER management with a

recommendation on how to implement. I can explain more tomorrow during our 1:1 in the afternoon -- would that work? If not, just let me know and we can touch base earlier.

Thx Grail

From: Woodcock, Janet
Sent: Tuesday, September 13, 2016 5:28 PM
To: Sipes, Grail
Subject: Fwd: Follow up on Eteplirsen

Do you know what kind of statutory requirement this is? Jw

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 13, 2016 at 3:57:39 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: [Borio, Luciana](#)
To: [Califf, Robert](#); [Woodcock, Janet](#); [Jenkins, John K](#); [Unger, Ellis](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 5:29:46 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN Borio.doc](#)

Dear Dr. Califf,

Thank you for the opportunity to review a draft of your decisional memo on Dr. Unger's appeal related to eteplirsen. Attached is a red-line version with some minor edits (to ensure accuracy) and two embedded comments. I have a few overarching comments that I include here:

- At several points your draft decisional memo erroneously attributes statements, views and conclusions of the SDR Board to me. Consistent with the SMG, the SDR Board recommendation memo reflects the consensus views of the SDR Board, which I communicated to you in my capacity as Chair. In accordance with the SMG, the recommendation memo would have documented any "minority views" expressed by members of the SDR Board. In this instance, there were no dissenting views. As such, contents of the SDR Board memo should be attributed to the SDR Board. The one exception is the section entitled "Considerations from the Acting Chief Scientist" on pages 25-26 of the SDR Board memo, where I speak in my capacity as Acting Chief Scientist.
- Your draft decisional memo erroneously suggests that the SDR Board expressed concerns or views about Dr. Woodcock's scientific conclusions. The SDR Board did not do so; it restricted its review to procedural issues.
- In footnote 23, you indicate that you were troubled by "Dr. Borio's suggestion" (see first bullet point) that Dr. Woodcock might have been motivated by financial considerations in rendering her decision. The "Procedural History" section of the SDR Board memo (pages 9-16) is not intended to set forth suggestions or conclusions by the SDR Board. Rather, it factually recites information gathered by the SDR Board during the course of its investigation of the procedural history of the scientific dispute within CDER. The paragraph you are referencing describes statements made by Dr. Woodcock during the SDR Board's interview of her. Likewise, the other parts of the procedural history simply summarize the administrative record and the views and recollections provided during interviews conducted by the SDR Board with Dr. Unger, the CDER Ombudsman, the review team member (who requested anonymity), and Dr. Woodcock.
- Lastly, your draft decisional memo seems to downplay the significance of the very small amount of dystrophin reported in the eteplirsen NDA (see, e.g., pages 4-5 of your draft decisional memo). In fact, your draft decisional memo never once cites the 0.3% increase in dystrophin production shown by Study 301 (or the 0.93% detected in Studies 201/202). Instead, your draft decisional memo attributes the scientific disagreement to: (1) a lack of consensus on the appropriate threshold for clinical

benefit both within CDER and in the scientific literature, and (2) concerns regarding the correlation between dystrophin production and clinical outcomes in Study 201/202. To me, the crux of the disagreement is not whether there is an appropriate threshold, but whether such a miniscule amount of dystrophin is reasonably likely to predict clinical benefit. Your draft decisional memo does not address that issue. In my view, it is not sufficient to say that no threshold has been established and that, therefore, any increase in dystrophin production is reasonably likely to predict clinical benefit.

I would be glad to discuss any concerns or questions you might have about my comments or suggested edits.

Sincerely,

Luciana Borio, M.D.
Acting Chief Scientist
Food and Drug Administration
White Oak Building 1, Room 3317
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-4637

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant

scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

Scientific Dispute Regarding Approval of Sarepta Therapeutics' Eteplirsen – Commissioner's Decision

(b) (5)



11 pages of draft language have been withheld as b(5) immediately following this page

From: [Jenkins, John K](#)
To: [Califf, Robert](#); [Woodcock, Janet](#); [Unger, Ellis](#); [Borio, Luciana](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 1:25:31 PM

Rob

I plan to provide feedback on your memo later today.

John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

From: [Califf, Robert](#)
To: [Jenkins, John K](#); [Woodcock, Janet](#); [Unger, Ellis](#)
Subject: RE: Follow up on Eteplirsen
Date: Tuesday, September 13, 2016 8:54:16 PM

Thx John. This is new to me so I'll seek advice and we'll discuss.

Regards

rmc

From: Jenkins, John K
Sent: Tuesday, September 13, 2016 3:58 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K

Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

3. Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

4. Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this

case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: [Rodriguez, Jennifer](#)
To: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#); [Conover, Katie](#); [Kraus, Tom](#)
Cc: [Woodcock, Janet](#)
Subject: RE: PLEASE SEE -- CDER Cleared Comms
Date: Tuesday, September 13, 2016 3:47:54 PM
Attachments: [Phase II approval reactive QA 09.13.16 CDER OMA.DOC](#)
Importance: High

All-

In looking at the most recent changes to the to Dr. Califf's memo, we made a few edits to the Phase II QA. Please let us know ASAP if you would like us to continue with these edits or keep what was originally in the QA.

Thanks!

Jen

From: Sherman, Rachel
Sent: Tuesday, September 13, 2016 2:10 PM
To: Rodriguez, Jennifer; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Welcome!

From: Rodriguez, Jennifer
Sent: Tuesday, September 13, 2016 2:03 PM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Thanks, Rachel! We will take a quick review of the comms against the most current version of RMC's memo to ensure there are no glaring contradictions or differences before sending it to HHS for review.

Thanks!

Jen

From: Sherman, Rachel
Sent: Tuesday, September 13, 2016 1:55 PM
To: Rodriguez, Jennifer; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Hi all,

I just poked me head into their meeting and have attached an edit on page as per Drs. Califf and Woodcock. So, this issue is resolved.

Rachel

From: Rodriguez, Jennifer
Sent: Tuesday, September 13, 2016 1:41 PM
To: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: PLEASE SEE -- CDER Cleared Comms
Importance: High

All,

Janet has reviewed the comms and had no edits on the press release or phase II QA. She has one comment and minor edits attached in the phase I KMQA (attached). I was told that Janet would be reaching out to talk to Califf directly about his comment on page 3. In the interest of time, we will proceed with sending up the comms to HHS by 2:30pm. If there are any edits (new QA) resulting from Janet and Dr. Califf's conversation we can make those at that time.

Please let me know by 2:30pm if you have any questions or concerns.

Best,
Jen

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, September 12, 2016 11:37 AM
To: Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert; Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: Re: PLEASE SEE -- Updated Comms

(b) (5)

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Rodriguez, Jennifer
Sent: Monday, September 12, 2016 10:17 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: PLEASE SEE -- Updated Comms

Hi All,

Attached please find the updated QAs, as well as the PR, reflecting the edits to date. In addition,

FDACDER000946

below please find a slightly revised response to the question about the review team. Please let me know if you would like us to go further.

Also, is it OK for us to reach out to Lu Borio's team to get the information for [REDACTED] (b) (5)

Once we have your OK, we will share the comms package with Chris Shreeve for CDER review – asking them to flag anything that is inaccurate or provides significant heart burn. We would like to be able to share with CDER by noon to keep on schedule.

Thanks for all your feedback.

Jen



From: Dickinson, Elizabeth (FDA)
Sent: Sunday, September 11, 2016 8:32 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie
Subject: RE: Q&A

(b) (5)

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

Nice job. These changes improve what I was trying to get across. Thanks.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

(b) (5)

FDACDER000948

From: Sherman, Rachel

Sent: Sunday, September 11, 2016 8:45 AM

To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.



Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

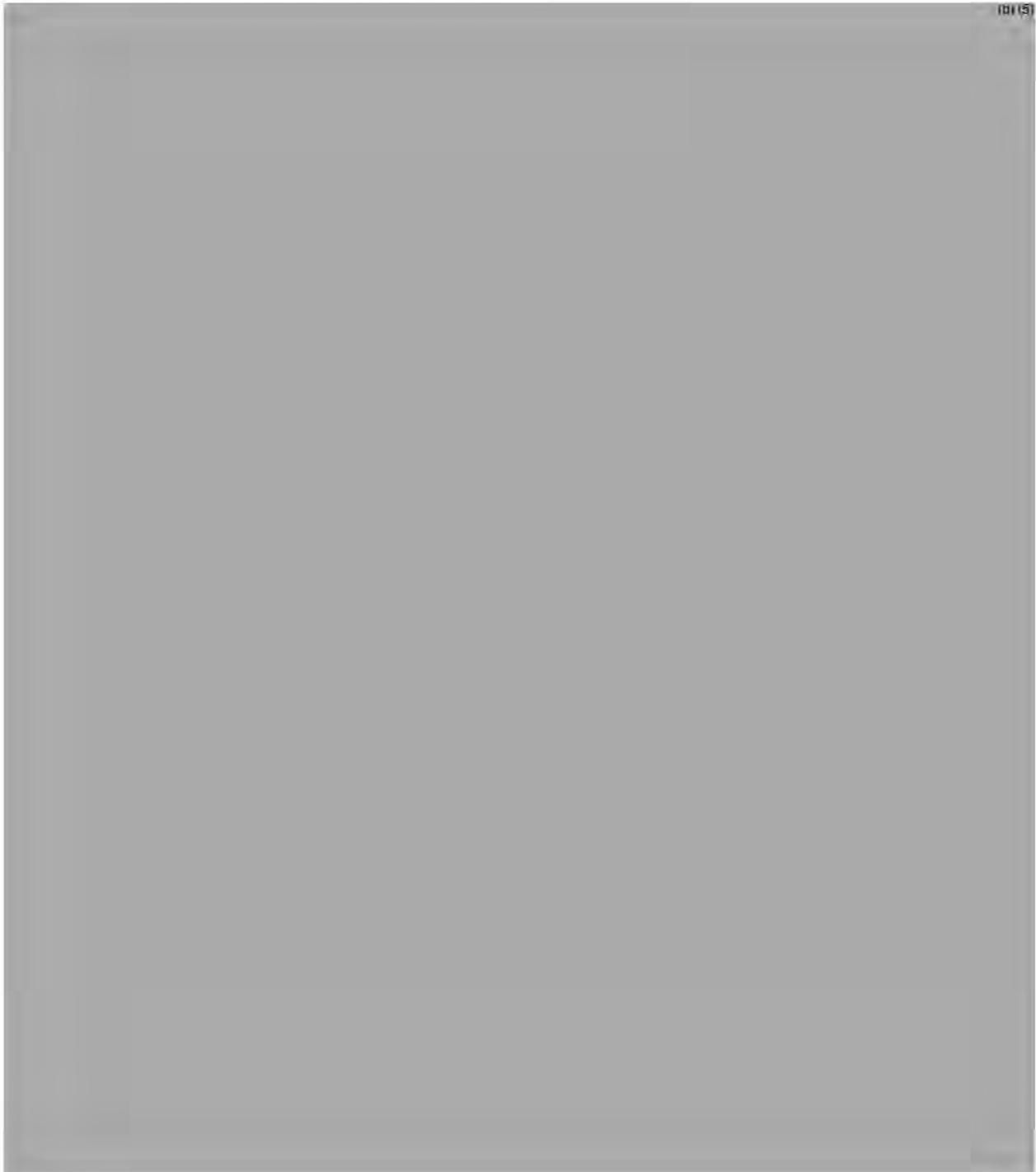
To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: Q&A

Friends,

I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:



(b) (5)



**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

(b) (5)



6 pages of draft language have been withheld as b(5) immediately following this page

From: [Califf, Robert](#)
To: [Woodcock, Janet](#); [Jenkins, John K](#); [Unger, Ellis](#); [Borio, Luciana](#)
Subject: memo
Date: Tuesday, September 13, 2016 6:40:06 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN.doc](#)

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

Message to Sarepta:

(b) (5)





IND/BLA/NDA: IND 077429/ NDA 206488
TO: Billy Dunn, M.D. (Director, Division of Neurology Products/ODE1)
FROM: Ashutosh Rao, Ph.D. (Laboratory Chief, DBRR III/OBP/OPQ/CDER)
THROUGH: Amy Rosenberg, M.D. (Director, DBRR III/OBP/OPQ/CDER)
Steven Kozlowski, M.D. (Director, OBP/OPQ/CDER)
SUBJECT: Review of dystrophin bioassays observed during inspection and related study report SR-CR-16-003
SPONSOR: Sarepta Therapeutics
PRODUCT: Eteplirsen (EXONDYS 51) is a phosphorodiamidate morpholino oligomer designed to bind to exon 51 of the human dystrophin pre-mRNA and intended to cause skipping of exon 51 to generate an internally truncated dystrophin protein. It is supplied as a 2 mL vial containing 100 mg (50 mg/mL) and single use 10 mL vial containing 500 mg (50 mg/mL) preservative-free solution.
INDICATION: For the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed gene mutation amenable to exon 51 skipping.
ROUTE OF ADMIN. Intravenous (IV) infusion
CLINICAL DIVISION: Division of Neurology Products (ODE1/OND/CDER)

Executive Summary:

The conduct of the western blotting procedure for the biopsy samples from study 4658-301 appeared to be within the scope of the sponsor's predetermined standard operating protocol SR-CR-16-003. The inspection confirmed technical compliance with the methodology, verified sample blinding throughout the procedure, confirmed that the procurement and analysis of raw data with passing acceptance criteria was used for % dystrophin calculations and successfully verified the same data in the study report '4658-301 Week 48 Interim Analysis' submitted to the agency.

The Sponsor could improve upon the robustness of the detection portion of the method by adopting automated and digitized detection systems and reference standards with lower variability in the future.

Background:

A limited, high-priority PDUFA inspection of a Sponsor's Laboratory Testing Site at Corvallis, OR, was conducted between June 20-24, 2016, upon request from the Division of Neurology Products, and per FACTS assignment # 11648400. The inspection assignment requested observation of the laboratory's conduct of a western blotting analytical procedure, real time confirmation of the integrity of the associated data generated from the procedure, as well as an assessment of the firm's adherence to their predefined protocols and blinding procedures. This inspection and the laboratory's performance of the western blotting procedures are associated with the Sponsor's study protocol 4658-301 (PROMOVI) titled, "An Open-Label, Multi-Center, 48-Week Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy". The study is being conducted under IND # 077429, in support of Sarepta Therapeutics, Inc.'s New Drug Application (NDA) # 206488. The inspection was conducted by myself and Young Moon Choi, Ph.D. (Lead Pharmacologist,

OSIS), and Mark Babbit (Investigator, ORA). This summary provided in this memo and requested by the Division of Neurology Products specifically addresses the dystrophin analytical aspects observed on site by me and a review of the report submitted by the Sponsor on 6/27/2016 based on the data obtained during inspection. The inspection did not include an assessment of Good Laboratory Practices or current Good Manufacturing Practices. Please refer to the Establishment Inspection Report (EIR) under the FEI number 3009712573 for a full description of the inspectional items.

For this purposes of this memo, the term ‘observation’ refers to the observed activities related to the bioassay method and not an objectionable compliance action. No objectionable FDA Form 483 observations were issued to the Sponsor. The first part of this memo summarizes the observations made during inspections regarding the control samples, western blotting procedure, dystrophin quantitation, and data analysis. The second part of the memo describes concurrence with the data set provided in study report SR-CR-16-003. It does not address the clinical efficacy or review the clinical interpretation of the % dystrophin values reported.

1. Summary of inspectional findings at Sarepta’s Corvallis, OR, Laboratory Testing Site that conducted an interim dystrophin analyses of biopsy samples from study 4658-301 (PROMOVI) by western blot:

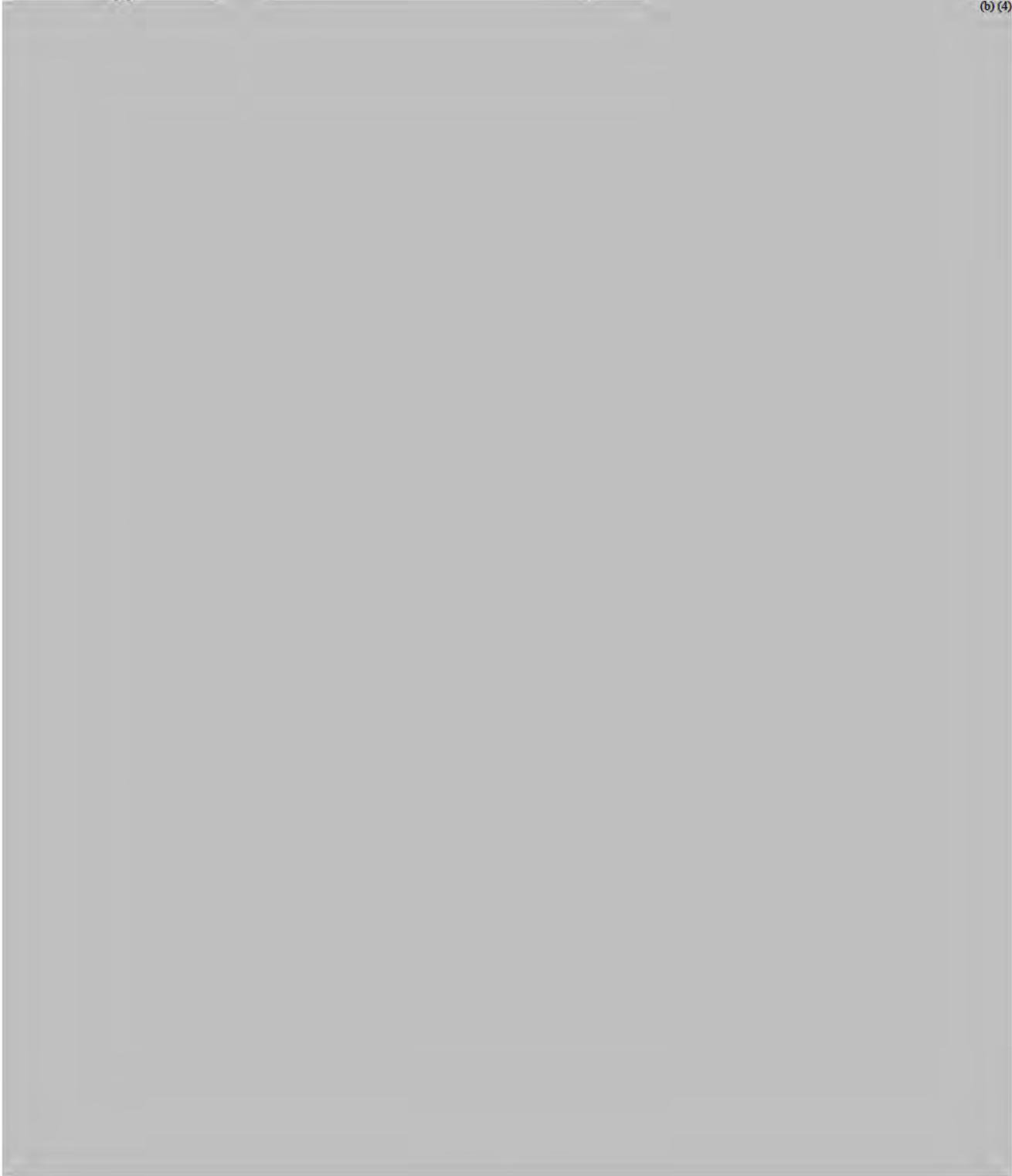
The finalized western blotting protocol SR-CR-16-003 and its appendices were used as a reference during the observation of the analytical procedure with samples from study 4658-301.

The control samples: The normal control NC-5 was originally designated as C14-23 and obtained from (b) (4) (b) (4) tissue bank (b) (4) NC-5 was obtained from the biceps of a 14 year old male at (b) (4) and as per the specimen report provided by the Sponsor, which noted that this subject had no pathological diagnosis. The sample NC-5 (b) (4) was used with the week 180 samples from study 202. (b) (4)

(b) (4) The untreated DMD controls were obtained from the PROMOVI study. Six untreated DMD samples were tested and the three with the lowest % dystrophin values were used as a pooled sample of the Negative Control. They were not from the week 48 but from the patients randomized to the week 24, 72, or 96 groups.

A copy of the Biopsy Specimen Collection and Examination Form was reviewed for each of the normal, DMD, and study 301 biopsy samples. The pathological examination was performed by (b) (4). It was noted that all samples were considered acceptable based on physical examination, measurement, absence of evidence of crushing by forceps, absence of freezing artifacts, fibrotic and/or adipose tissue content using H&E stained sections, and fiber orientation. No samples appear to be rejected based on the quality assessment in their tissue allocation SOP. A copy of the exon mutations and patient ages of each of the blinded samples was provided by the Sponsor, without reference to the sample identification.

Sample designation and western blot procedure: Each pair of blinded, individual patient samples were randomized and randomly labeled as either 'Ford' or 'Chevy' (b) (4). The samples were shipped from (b) (4) and stored at -20°C at Corvallis, OR. (b) (4)



Quantitation of images and data analyses: Each of the films was analyzed for dystrophin band density with ImageQuant (version 8.1) software (b) (4). A PowerPoint presentation with each of the steps involved and as observed on June 21-24 was provided by the Sponsor.

(b) (4)

The Microsoft Excel table print-outs provided by the Sponsor showed the interim analysis with raw numbers of % dystrophin the R-square value whether the R-square value was a pass or fail

(b) (4)



At the end of the inspection, two CD-ROMs were provided by Mr. Voss with all raw and analyzed data files. The inspection was closed with a scientific discussion with (b) (4) (b) (4) John Voss, M.S., and (b) (4) about (1) need for improvement of the current western blotting with a more robust detection and quantitation method that allows consistent quantitation at low levels of dystrophin, (2) the need for more robust assays, such as quantitative mass spectrometry, with greater precision and (3) the need for a more reliable reference standard, such as recombinant protein or cell line-based extracts, with lower inherent variability to allow precise quantitation of relative % normal dystrophin. The Sponsor acknowledged the feedback and stated that they are in the process of further developing their protein analyses methods and will be submitting a proposal for using a skeletal muscle myoblast cell line-based reference standard in the near future.

Reviewer's comments: The western blotting procedure for the biopsy samples appeared to have been conducted within the scope of the sponsor's predetermined standard operating procedures. I and the other FDA inspectors followed the western blotting procedure from the removal of samples from the freezer to the densitometric quantitation and did not observe any inappropriate manipulation. At no point did we have reason to believe that the sample blinding was compromised. The technicians were observed to be diligent and competent in the performance of the bioassay. The Sponsor could improve upon the consistency of the detection portion of the method and was advised to consider other more robust detection systems and reference standards in the future. Each of the additional analyses conducted in our presence, such as the overlaid chromatogram traces, appeared to be obtained with a sound scientific justification of its usefulness to clarify the relative dystrophin levels between the samples as observed with the protocol.

2. Review of dystrophin bioassay information from study 4658-301 in Sarepta's NDA amendment 42 and study report SR-CR-16-003 submitted on 6/27/2016:

Based on a review of the study report SR-CR-16-003, I was able to match each of the data points that passed acceptance criteria and used for their data table on page 17 (**Appendix 5**).

Powerpoint slides were provided to the Division of Neurology Products (Dr. Ron Farkas) on 6/28/2016 showing a line-by-line comparison of each of the data points with QC-checked summary tables we were provided during the on-site inspection.

The following data points from the failed gels didn't match the summary data table I had from the inspection but did match the original worksheet from the technicians. Neither of these data points was used in the analyses by the sponsor because these are from failed gels so they should not impact any of the mean values.

1. Patient ID 301-07, Gel 13, we were given 0 and 0 as the numbers for lane 7 and 8. The sponsor has reported 0.04 and 0.22. The original data worksheet confirms 0.04 and 0.22. This gel failed its R-square acceptance criteria so this data point is not included in the sponsor's analysis.
2. Patient ID 301-12, Gel 24, we were given 0.02 as the value for Lane 7. The sponsor has reported 0.01. The original data worksheet confirms 0.01. This gel failed its R-square acceptance criteria so this data point is not included in the sponsor's analysis.

Reviewer's comments: The raw % dystrophin data that passed predefined acceptance criteria and submitted by the Sponsor was in agreement with the raw data obtained on site at the Corvallis, OR, testing laboratory. The two exceptions noted above for the data that failed quality control assessments were in agreement with the original data worksheets and not used for calculation of the % dystrophin values and hence should not impact the overall findings.

The Division of Neurology Products (ODEI/OND) will be conducting a review of the clinical efficacy and interpretation of the clinical implications of the % dystrophin findings.

Appendix 1

Western blot analysis schedule and sample loading sequence of the gels (provided by Sarepta)

WESTERN BLOT ANALYSIS SCHEDULE

DAY 1-2: JUNE 20 & 21 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
1	1a	HMW	4%	2%	1%	0.5%	0.25%	Ford-22559 (1.5X)	Chevy-22559 (1.5X)	Neg Ctrl	HMW
2	1b	HMW	4%	2%	1%	0.5%	0.25%	Ford-22559 (1.5X)	Chevy-22559 (1.5X)	Neg Ctrl	HMW
3	2a	HMW	4%	2%	1%	0.5%	0.25%	Ford-27336 (2X)	Chevy-27336 (2X)	Neg Ctrl	HMW
4	2b	HMW	4%	2%	1%	0.5%	0.25%	Ford-27336 (2X)	Chevy-27336 (2X)	Neg Ctrl	HMW
5	3a	HMW	4%	2%	1%	0.5%	0.25%	Ford-24422 (1X)	Chevy-24422 (2X)	Neg Ctrl	HMW
6	3b	HMW	4%	2%	1%	0.5%	0.25%	Ford-24422 (1X)	Chevy-24422 (2X)	Neg Ctrl	HMW
7	4a	HMW	4%	2%	1%	0.5%	0.25%	Ford-27138 (1X)	Chevy-27138 (1X)	Neg Ctrl	HMW
8	4b	HMW	4%	2%	1%	0.5%	0.25%	Ford-27138 (1X)	Chevy-27138 (1X)	Neg Ctrl	HMW
9	5a	HMW	4%	2%	1%	0.5%	0.25%	Ford-28500 (2.5X)	Chevy-28500 (1X)	Neg Ctrl	HMW
10	5b	HMW	4%	2%	1%	0.5%	0.25%	Ford-28500 (2.5X)	Chevy-28500 (1X)	Neg Ctrl	HMW
11	6a	HMW	4%	2%	1%	0.5%	0.25%	Ford-24986 (1X)	Chevy-24986 (2X)	Neg Ctrl	HMW
12	6b	HMW	4%	2%	1%	0.5%	0.25%	Ford-24986 (1X)	Chevy-24986 (2X)	Neg Ctrl	HMW

DAY 3-4: JUNE 22 & 23 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
13	1a	HMW	4%	2%	1%	0.5%	0.25%	Ford-20841 (1X)	Chevy-20841 (2X)	Neg Ctrl	HMW
14	1b	HMW	4%	2%	1%	0.5%	0.25%	Ford-20841 (1X)	Chevy-20841 (2X)	Neg Ctrl	HMW
15	2a	HMW	4%	2%	1%	0.5%	0.25%	Ford-22355 (1.5X)	Chevy-22355 (1.5X)	Neg Ctrl	HMW
16	2b	HMW	4%	2%	1%	0.5%	0.25%	Ford-22355 (1.5X)	Chevy-22355 (1.5X)	Neg Ctrl	HMW
17	3a	HMW	4%	2%	1%	0.5%	0.25%	Ford-28907 (2X)	Chevy-28907 (1X)	Neg Ctrl	HMW
18	3b	HMW	4%	2%	1%	0.5%	0.25%	Ford-28907 (2X)	Chevy-28907 (1X)	Neg Ctrl	HMW
19	4a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29648 (2X)	Chevy-29648 (2X)	Neg Ctrl	HMW
20	4b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29648 (2X)	Chevy-29648 (2X)	Neg Ctrl	HMW
21	5a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29727 (1X)	Chevy-29727 (1X)	Neg Ctrl	HMW
22	5b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29727 (1X)	Chevy-29727 (1X)	Neg Ctrl	HMW
23	6a	HMW	4%	2%	1%	0.5%	0.25%	Ford-29751 (1X)	Chevy-29751 (1X)	Neg Ctrl	HMW
24	6b	HMW	4%	2%	1%	0.5%	0.25%	Ford-29751 (1X)	Chevy-29751 (1X)	Neg Ctrl	HMW

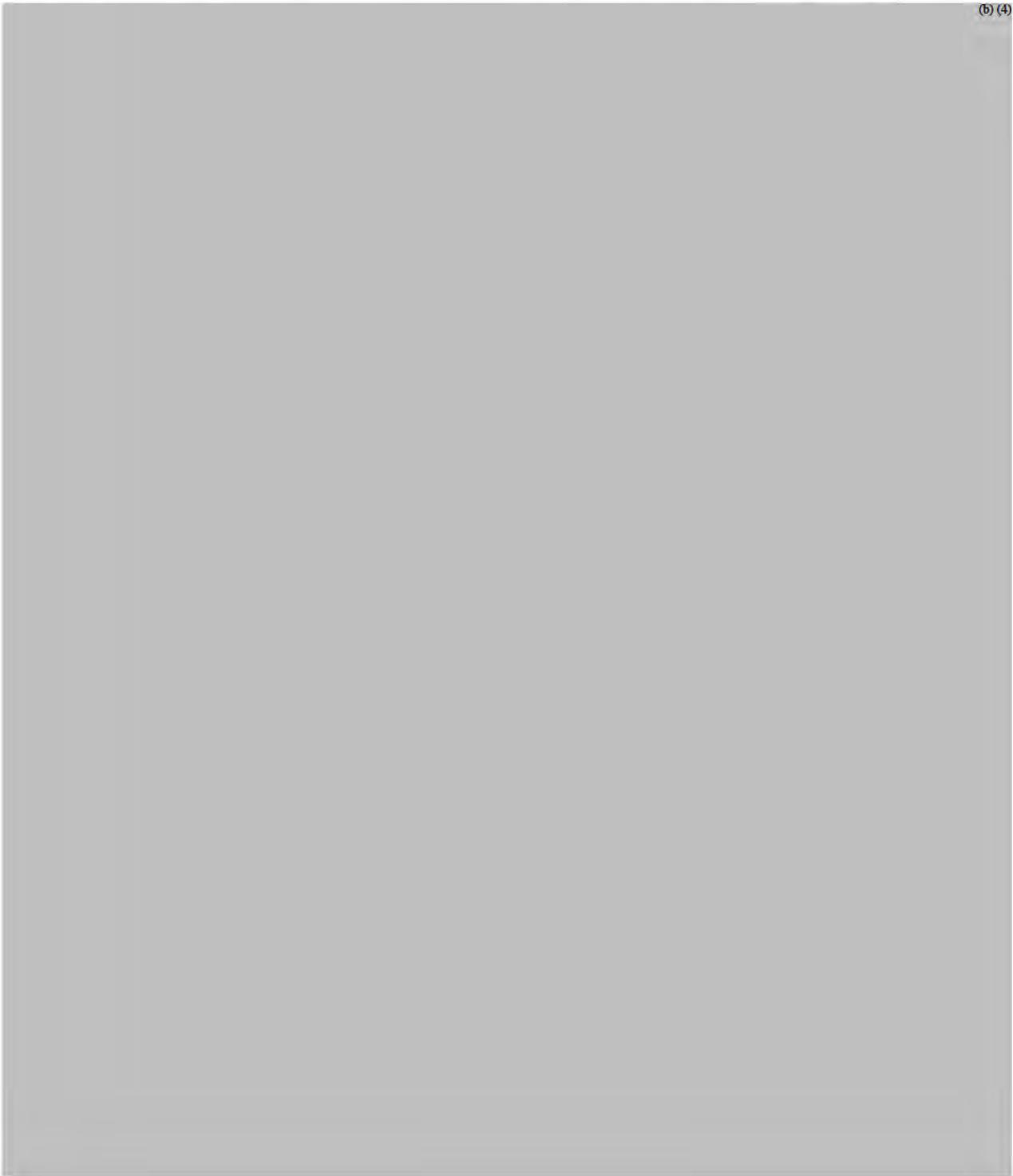
WESTERN BLOT ANALYSIS SCHEDULE

DAY 3-4: JUNE 22 & 23 2016

Gel #	Box	Lane									
		1	2	3	4	5	6	7	8	9	10
25	7a	HMW	4%	2%	1%	0.5%	0.25%	Ford-25715 (1X)	Chevy-25715 (2X)	Neg Ctrl	HMW
26	7b	HMW	4%	2%	1%	0.5%	0.25%	Ford-25715 (1X)	Chevy-25715 (2X)	Neg Ctrl	HMW

Appendix 2

Raw dystrophin antibody-probed membranes for each of the western blot samples (Images provided by Sarepta)



Appendix 3

Three examples of chromatographic traces of the dystrophin quantitation from Lanes 7 and 8 using ImageQuant software (provided by Sarepta)

Image Filename: SR-CR-16-003_Gel#5_DYS1_30min.tif

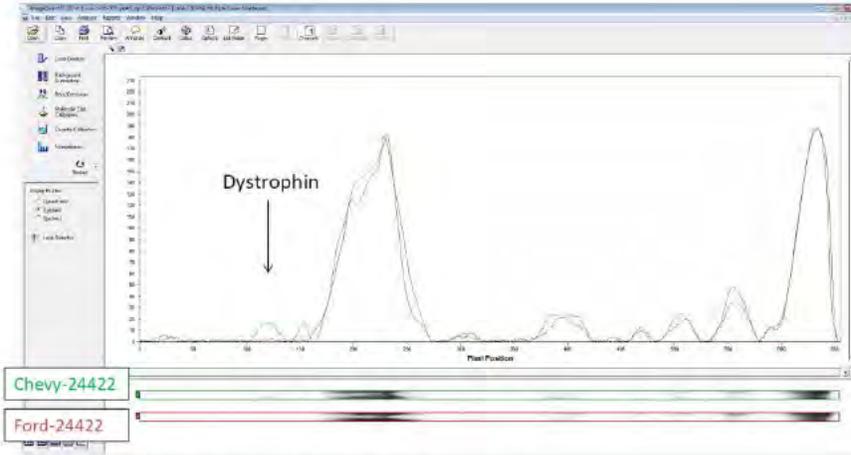


Image Filename: SR-CR-16-003_Gel#9_DYS1_30min.tif

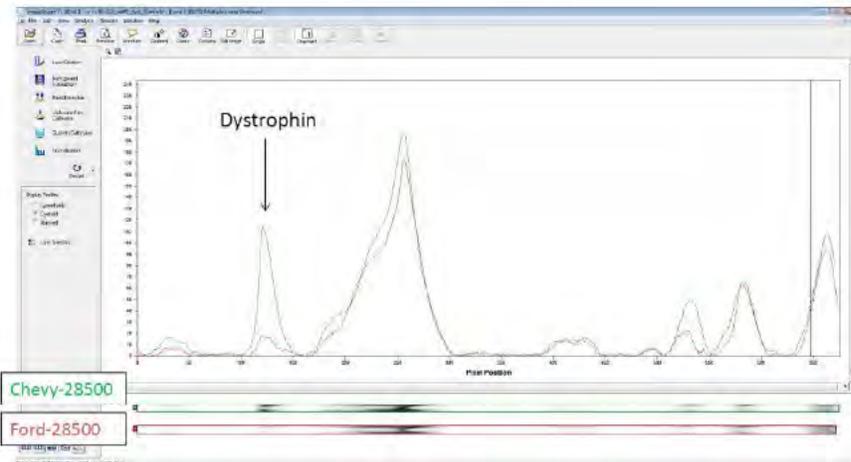
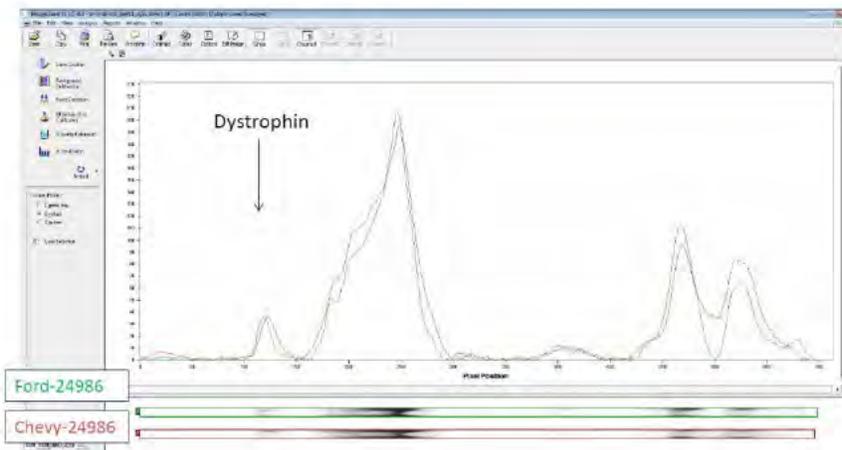


Image Filename: SR-CR-16-003_Gel#11_DYS1_30min.tif



Appendix 4

Summary raw data tables showing all individual data points and whether they passed or failed acceptance criteria from the 15, 20, or 30 minute film exposures (Three tables below provided by Sarepta)

SR-CR-16-003: DYS1 - 15 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
13	1a	0.00	0.00	0.38	Fail	67389 (47602)	Pass
14	1b	0.17	0.42	0.97	Pass	64418 (58077)	Pass
15	2a	0.08	0.08	0.95	Pass	37476 (58536)	Fail
16	2b	0.14	0.05	0.83	Fail	21696 (20615)	Pass
17	3a	1.17	0.14	0.98	Pass	22073 (35280)	Fail
18	3b	1.57	0.24	0.98	Pass	49106 (37627)	Pass
19	4a	0.11	0.12	0.93	Pass	40030 (8873)	Pass
20	4b	0.05	0.11	0.98	Pass	35884 (39241)	Fail
21	5a	0.31	0.01	0.98	Pass	110706 (48990)	Pass
22	5b	0.63	0.08	0.93	Pass	93278 (52055)	Pass
23	6a	0.09	0.02	0.91	Pass	77556 (51352)	Pass
24	6b	0.02	0.00	0.78	Fail	108111 (64389)	Pass
25	8a	0.34	0.34	0.96	Pass	38943 (83782)	Fail
26	8b	0.18	0.21	0.97	Pass	20460 (19812)	Pass

SR-CR-16-003: DYS1 - 20 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
1	1a	0.14	0.27	0.99	Pass	14425 (8649)	Pass
2	1b	0.07	0.21	0.96	Pass	39798 (15235)	Pass
3	2a	0.36	0.35	0.99	Pass	26926 (14147)	Pass
4	2b	0.10	0.12	0.90	Pass	47296 (73361)	Fail
5	3a	0.13	0.50	0.98	Pass	22397 (31305)	Fail
6	3b	0.09	0.22	1.00	Pass	64945 (29089)	Pass
7	4a	0.04	0.08	0.95	Pass	44795 (16235)	Pass
8	4b	0.04	0.13	0.89	Fail	60880 (35534)	Pass
9	5a	0.10	1.08	0.80	Fail	86479 (40898)	Pass
10	5b	0.07	0.74	1.00	Pass	33696 (13462)	Pass
11	6a	0.30	0.37	0.97	Pass	31429 (30177)	Pass
12	6b	0.15	0.18	0.94	Pass	23477 (32971)	Fail
13	1a	0.01	0.01	0.11	Fail	87486 (71878)	Pass
14	1b	0.02	0.23	0.96	Pass	114817 (88315)	Pass
15	2a	0.04	0.05	0.90	Pass	82129 (91951)	Pass
16	2b	0.34	0.06	0.72	Fail	41439 (28302)	Pass
17	3a	0.91	0.08	0.99	Pass	78991 (47683)	Pass
18	3b	2.01	0.47	0.79	Fail	72064 (110397)	Fail
19	4a	0.01	0.22	0.91	Pass	78641 (33905)	Pass
20	4b	0.01	0.03	0.93	Pass	79184 (88118)	Fail
21	5a	0.09	0.00	0.75	Fail	187873 (38528)	Pass
22	5b	0.54	0.02	0.94	Pass	127964 (74633)	Pass
23	6a	0.00	0.00	0.80	Fail	131413 (58017)	Pass
24	6b	0.00	0.00	0.10	Fail	133242 (88876)	Pass
25	8a	0.20	0.32	0.65	Fail	33377 (88614)	Fail
26	8b	0.08	0.08	0.91	Pass	39914 (30132)	Pass

SR-CR-16-003: DYS1 - 30 minute exposure							
Gel	Box	% Dystrophin (Lane 7)	% Dystrophin (Lane 8)	R2 Value	R2 ≥ 0.90	0.25%NC (Neg CT)	Neg CT <0.25%
1	1a	0.15	0.22	0.98	Pass	28142 (11562)	Pass
2	1b	0.11	0.29	0.99	Pass	43028 (10859)	Pass
3	2a	0.49	0.50	0.96	Pass	25657 (32471)	Fail
4	2b	0.12	0.26	0.92	Pass	49843 (76849)	Fail
5	3a	0.06	0.50	0.99	Pass	25008 (24738)	Pass
6	3b	0.06	0.24	0.99	Pass	64307 (34135)	Pass
7	4a	0.04	0.10	0.96	Pass	41141 (20779)	Pass
8	4b	0.06	0.19	0.83	Fail	51902 (41555)	Pass
9	5a	0.10	0.92	0.87	Fail	97732 (52789)	Pass
10	5b	0.17	1.02	0.98	Pass	60795 (11082)	Pass
11	6a	0.42	0.48	0.96	Pass	32341 (37122)	Fail
12	6b	0.29	0.46	0.96	Pass	29677 (34028)	Fail
13	1a	0.21	0.33	0.74	Fail	57768 (65008)	Fail
14	1b	0.04	0.77	0.70	Fail	102231 (81450)	Pass
15	2a	0.03	0.03	0.91	Pass	76752 (110138)	Fail
16	2b	0.34	0.04	0.71	Fail	46083 (40425)	Pass
17	3a	1.11	0.08	0.96	Pass	60216 (61057)	Fail
18	3b	3.91	0.48	0.99	Pass	81999 (89679)	Fail
19	4a	0.09	0.15	0.93	Pass	58708 (28376)	Pass
20	4b	0.00	0.05	0.95	Pass	66033 (80195)	Fail
21	5a	0.11	0.00	0.28	Fail	175676 (80890)	Pass
22	5b	0.49	0.03	0.92	Pass	110870 (50983)	Pass
23	6a	0.02	0.00	0.86	Fail	95415 (92390)	Pass
24	6b	0.00	0.00	0.19	Fail	127200 (95678)	Pass
25	8a	0.10	0.11	0.28	Fail	48731 (108832)	Fail
26	8b	0.04	0.08	0.90	Pass	42916 (29626)	Pass

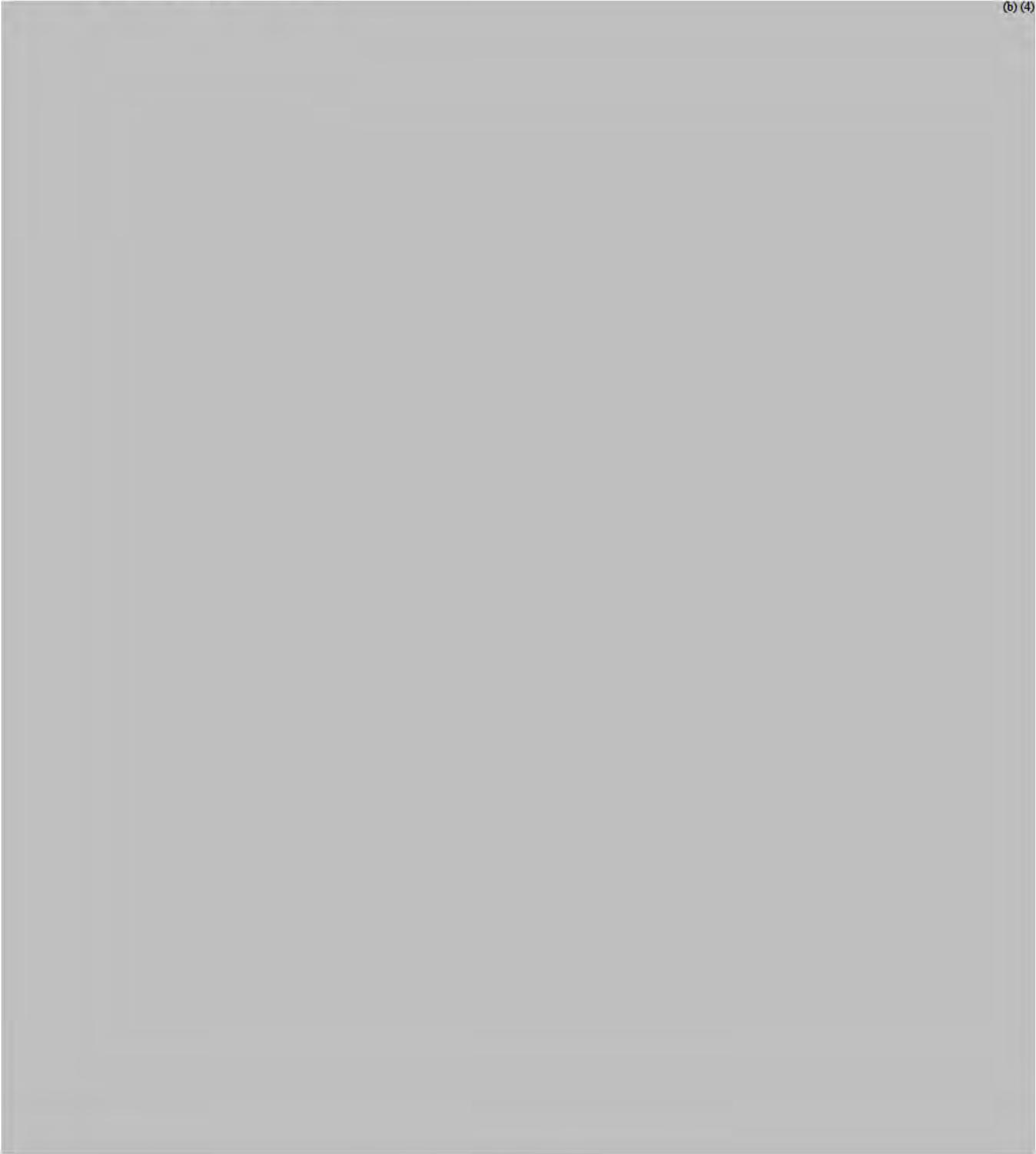
Appendix 5

Data listing from report 4658-301-SR-CR-16 of Dystrophin Western blot results with all raw values (provided by Sarepta)

SR-CR-16-003 Patient WB Analysis
4658-301 Week 48 Interim Analysis

June 27, 2016

(b) (4)



Office of Drug Evaluation-I: Decisional Memo

Date	July 15, 2016
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	206488
Applicant Name	Sarepta Therapeutics
Date of Submission	June 26, 2015
PDUFA Goal Date	May 26, 2016 (post-3-month extension for major amendment)
Proprietary Name/ Established (USAN) Name	EXONDYS 51™ eteplirsen injection
Dosage Forms/ Strengths	2 mL single-use vials containing 100 mg (50 mg/mL) eteplirsen 10 mL single-use vials containing 500 mg (50 mg/mL) eteplirsen
Indication originally sought by applicant (see page 29 for final)	“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials.”
Action:	<i>Complete response</i>

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Yuet (Fannie) Choy, Laurie Kelley
Medical Officer/Clinical	Christopher Breder
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, Ta-Chen Wu, Hobart Rogers, Kevin Krudys, Angela Men, Christian Grimstein, Meहुल Mehta
Statistical Review	Xiang Ling, Kun Jin, Hsien Ming (Jim) Hung
Pharmacology Toxicology	David Hawver, Lois Freed, Paul Brown
Office of Biotechnology Products	Ashutosh Rao, Amy Rosenberg
Office of New Drug Quality Assessment	Joseph Leginus, Mari Chelliah, Sung Kim, Denise Miller, Zhong Li, Dahlia Woody, Martha Heimann, James Laurensen, Donna Christner, Neal Sweeney, Edwin Jao, Zhihao Peter Qiu, Wendy Wilson-Lee, M. Scott Furness
Office of Scientific Investigations	Antoine El Hage, Cara Alfaro, Susan Thompson, Kassa Ayalew, Ni Aye Khin
Method Validation	Michael Hadwiger, Michael Trehу
Statistical Review – Stability data	Zhuang Miao, Xiaoyu Dong, Meiyu Shen, Yi Tsong
Office of Prescription Drug Promotion	Aline Moukhtara
Division of Medication Error Prevention and Analysis	Deborah Meyers, Justine Harris, Danielle Harris, Todd Bridges
Division of Risk Management	Robert Pratt, Jamie Parker, Kellie Taylor, Cynthia LaCivita
Associate Director for Labeling	Tracy Peters
Cross-Discipline Team Leader	Ronald Farkas
Deputy Director, Division of Neurology Products	Eric Bastings

1. Introduction

Sarepta Therapeutics is seeking accelerated approval for eteplirsen for the proposed indication:

“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials.”

I agree with the views of the Division of Neurology Products (DNP), the Office of Biometrics, and the Office of Clinical Pharmacology that the applicant has not provided substantial evidence of effectiveness from adequate and well controlled trials to support conventional approval. I also agree that the applicant has not provided support for accelerated approval, i.e., evidence from adequate and well controlled trials of an effect on a biomarker that is reasonably likely to predict effectiveness. Thus, I agree with the DNP recommendation to issue a *Complete Response* for this application.

2. Background

Description:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, restoration of the mRNA reading frame would permit translation of an internally truncated, but nevertheless functional form of the dystrophin protein. The drug is targeted specifically for patients with DMD “who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.” It is not clear which of the specific mutations are amenable to exon 51 skipping.

PMOs are a class of synthetic molecules based upon a redesign of the natural nucleic acid structure. They are distinguished from native DNA and RNA because of a 6-membered morpholino ring that replaces the 5-membered ring found in native DNA and RNA. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in native DNA and RNA. Each morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10.3 kilodaltons.

Disease Background:

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene located on the short arm of the X chromosome. These mutations disrupt the mRNA reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys (~1 in 10,000 to 14,000 males). Patients who are amenable to skipping exon 51 constitute ~13% of the DMD patient population.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix, and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Currently, glucocorticoid therapy is the cornerstone of clinical management, and is widely believed to delay loss of ambulation and respiratory decline by several years. Ventilatory assistance and physiotherapy are also thought to improve survival for DMD patients.

3. Product Quality

From a product quality perspective, NDA 206488 is recommended for approval. Eteplirsen would be marketed as a sterile, aqueous, preservative-free, concentrated solution for dilution prior to IV administration, to be supplied in single-use glass vials containing 100 mg or 500 mg eteplirsen (50 mg/mL).

OPQ recommends the following post-marketing commitments (PMCs), to be fulfilled no later than one year following NDA approval:

1. Investigate the root cause of the increasing assay trend observed in the drug product stability study.
2. Revalidate the accuracy of the in-process (b) (4) method used during drug product manufacture.
3. Revalidate the robustness of the in-process (b) (4) method in terms of (b) (4) (b) (4).
4. Investigate the consistent bias in the in-process (b) (4) results and the release (b) (4) (b) (4) results.

4. Nonclinical Pharmacology/Toxicology:

From a nonclinical perspective, NDA 206488 is recommended for approval. Pivotal toxicology studies were conducted in male monkeys (39-week study) and juvenile male rats (10-week study). A 26-week study was conducted in male transgenic mdx mice using a mouse-specific surrogate (AVI-4225). In all 3 species, the kidney was identified as the 1° target organ, with dose-dependent renal tubular cytoplasmic basophilia and/or vacuolation and tubular degeneration and necrosis, primarily at the highest doses tested.

Dilatation of the lateral ventricles of the brain was observed at mid and high doses in the *mdx* mouse study. The mechanism of this effect and its relevance to humans are unknown. In juvenile rats, slight reductions in bone length, width, area, mineral content, and mineral density were observed at the high dose. These concerns could lead to recommendations for long-term monitoring in patients.

Mean eteplirsen plasma exposures (AUC) at the no observed adverse effect levels (NOAELs) for monkeys and juvenile rats were 20- and 6-fold, respectively, higher than that of patients who received the to-be-marketed dose of 30 mg/kg/week by the intravenous route.

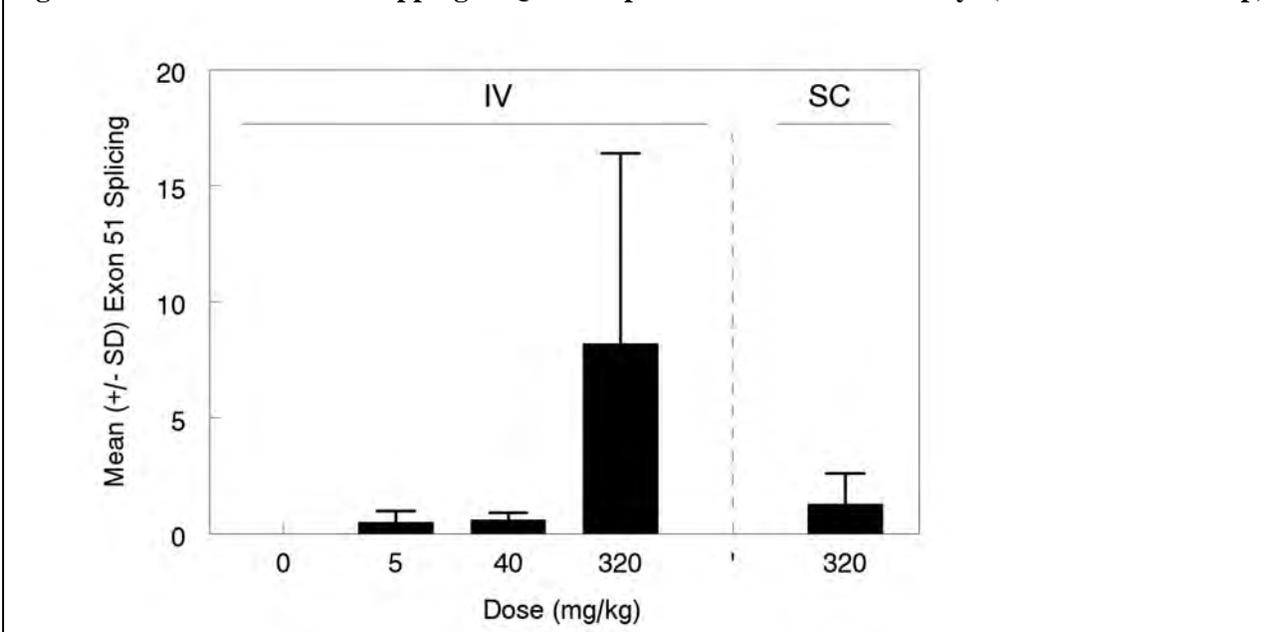
The applicant presented data on the exon skipping activity of eteplirsen in cynomolgus monkeys (“Exon skipping activity of AVI-4658 in cynomolgus monkey tissue samples from ^{(b) (4)} study ^{(b) (4)},” applicant study 4658-ssa-005). Samples of quadriceps muscle, heart, and diaphragm tissues were collected on Day 79 from cynomolgus monkeys after 12 weekly doses of eteplirsen at 0, 5, 40, or 320 mg/kg IV, or 320 mg/kg SC. Muscle samples were analyzed for exon 51 skipping of the dystrophin gene using polymerase chain reaction (PCR).

Exon skipping was detected in a nonlinear, dose-dependent manner (Table 1, Figure 1). With a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. As noted below, the applicant studied doses of 30 and 50 mg/kg/week in the clinic (6 patients at each dose), and there is significant question as to whether the plateau of the dose-response curve was reached. It is possible that much higher doses could lead to substantially greater effects on dystrophin production – effects that could be important for efficacy.

Table 1: Average Percentage of Exon 51 Skipping in Intact Monkeys (N=8 for Each Group)

Tissue	Average % Exon 51 Splicing ±SD				
	0 mg/kg IV	5 mg/kg IV	40 mg/kg IV	320 mg/kg IV	320 mg/kg SC
Quadriceps muscle	0.0 ± 0.0	0.5 ± 0.5	0.6 ± 0.3	8.2 ± 7.4	1.3 ± 0.5
Heart	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.2	4.5 ± 2.9	1.4 ± 0.5
Diaphragm	0.0 ± 0.0	0.2 ± 0.2	0.9 ± 0.7	6.1 ± 3.5	2.2 ± 0.9

Figure 1: Evidence of Exon Skipping in Quadriceps Muscle in Intact Monkeys (N=8 for Each Group)



With respect to the advisability of evaluating higher doses in humans, this subject is well summarized by Dr. Bastings in his Division Memo: “Considering the seriousness of DMD, the unmet medical need, and the nature of the toxicities observed in animals, I believe that the nonclinical data would support, with proper monitoring, dosing in DMD patients at least up to 200 mg/kg, a dose expected to provide exposure similar to the most sensitive species NOAEL for the toxicities seen in animals. If the human safety experience at these doses is acceptable, further dose escalation is possible in DMD patients.”

Finally, the nonclinical review team provided insight that is relevant for the interpretation of clinical data with respect to production of dystrophin protein: “The most robust finding among the studies provided and referenced in this submission was the wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients.”

Carcinogenicity:

Carcinogenicity studies have not been conducted with eteplirsen. The nonclinical review team opined that carcinogenicity studies in 2 species should be conducted as a post-marketing requirement. Dr. Bastings agrees, and I agree, that for this serious indication with unmet need, carcinogenicity studies can be deferred until after marketing.

5. Clinical Pharmacology

The Clinical Pharmacology team does not recommend approval; they recommend generation of robust evidence of effectiveness prior to approval. Specifically, the team is recommending a double-blind, placebo-controlled study in patients with mutations amenable to exon-51 skipping who are likely to be ambulant for 1 year, with use of appropriate endpoints based on upper or lower body strength in patients between 4 and 12 years of age. They also suggest study of doses greater than 50 mg/kg administered weekly, or alternate regimens that would include loading and maintenance doses, for example, twice-weekly administration for 6 months followed by weekly administration for 6 months. Their recommendations are based on the 3- to 4-hour half-life of the drug, urinary excretion of 60-70% of the drug within 24 hours, and the absence of known toxicity at doses of 50 mg/kg. The immunogenicity of eteplirsen can be further assessed in future clinical trial(s) as well.

Summary of Pharmacokinetics:

- Pharmacokinetics was approximately dose-proportional and linear from 0.5 to 50 mg/kg/week, with insignificant accumulation in this dose range.
- Following single or multiple intravenous infusions, peak plasma concentrations (C_{max}) occurred near the end of infusion.
- Plasma concentration-time profiles showed multi-phasic decline, with virtually all drug eliminated within 24 hours (24 hours after completion of infusion, eteplirsen concentrations were 0.02% of C_{max}).
- At doses of 30 and 50 mg/kg, the elimination half-life is ~3.5 hours, with ~65% of the drug excreted unchanged in the urine. The drug is not metabolized.
- Protein binding of eteplirsen in humans is relatively low, ~6% to 17%, and is independent of concentration.

- The volume of distribution data suggest distribution or cellular uptake into peripheral tissues.
- Inter-subject pharmacokinetic variability is moderate, generally in the range of 20 to 55% for exposure measures (C_{max} and AUCs) as well as other key pharmacokinetic parameters.
- Intrinsic factors were not studied (typically, in a larger development program, age, gender, body weight, geographic region, hepatic impairment, renal impairment, and other potentially significant covariates would be studied).
- *In vitro* investigations on major CYP isozymes and transporters did not reveal the need for additional investigation in humans.
- Eteplirsen was not a significant inhibitor or inducer of CYP.
- Eteplirsen was not a substrate or inhibitor for any of the key human transporters tested.
- Eteplirsen is expected to have a low potential for drug-drug interactions.

Finally, the clinical pharmacology team noted that if eteplirsen were found to be safe and effective, it would likely benefit all mutations amenable to exon-51 skipping and should be labeled accordingly.

QT Effects:

QT effects were not formally investigated in man.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

Sarepta is seeking accelerated approval for eteplirsen for the proposed indication:

“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [*see Clinical Studies (14)*]. Continued benefit will be evaluated through confirmatory trials.”

In this section, I provide an explanation of how accelerated approval might be used as a potential pathway to approval, based on production of dystrophin in skeletal muscle. I then discuss the evidence that eteplirsen produces dystrophin in skeletal muscle, based on immunohistochemistry and Western blot analyses. Finally, I discuss the clinical data that could serve as the basis for a conventional approval.

Accelerated Approval:

The applicant has requested accelerated approval based on an endpoint of 6-minute walk distance. The proposed indication states that 6-minute walk test is considered to be an intermediate endpoint demonstrating delayed disease progression.

There is little in the NDA to explain the applicant’s thought process here. In Sarepta’s briefing materials for the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, they stated (page 16):

“The accelerated approval pathway means that there will be an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty is addressed by the requirement that ‘appropriate post-approval studies to verify and describe the predicted effect’ would usually be underway at the time of approval.”

The applicant appears to misconstrue the intent of the accelerated approval pathway. They purport to show that, after 36 months of treatment, eteplirsen improves physical performance as assessed by the 6-minute walk test. We consider the 6-minute walk test to be a valid and meaningful measure of how well a patient functions – i.e., a clinical endpoint that would be a basis for full approval – not a surrogate endpoint or an intermediate endpoint. For slowly progressive diseases, an intermediate clinical endpoint, a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug’s effect on irreversible morbidity or mortality or other clinical benefit, can be used to support accelerated approval. But all would agree that showing an improvement on a clinically meaningful endpoint at 36 months would be adequate to support a conventional approval in DMD, a position we have taken with other DMD drugs.

Thus, the applicant has provided study results that purport to show improvement in a meaningful clinical endpoint after a relatively long duration of treatment, but they appear to propose accelerated approval as a means to deal with uncertainty about whether the therapy has actually been shown to provide a clinical benefit in the trial.

Clearly, if the review team had reached the conclusion that the applicant had provided substantial evidence of an effect on 6-minute walk distance during some 3 to 3.5 years of treatment, they would recommend a conventional (full) approval, and not accelerated approval. As noted in the reviews, however, for a number of reasons the review team does not believe that the applicant has provided substantial evidence of an effect on 6-minute walk distance, or any measure of physical performance (see below). Importantly, accelerated approval is not intended to enable use of less than substantial evidence of a treatment effect as a basis for approval, to be bolstered by more compelling evidence to be developed in the post-marketing setting.

Despite the lack of substantial evidence of clinical efficacy from Study 201/202 (see below), it is important to consider whether accelerated approval, based on an effect on a surrogate endpoint, could provide a viable alternative pathway to approval. The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept “...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological,

pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 3) whether the effect demonstrated meets the test of being “reasonably likely” to predict clinical benefit.

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for the demonstration of effectiveness, but this is not correct. Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These requirements have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

Again, the critical issue here is whether factor 3 (above) is met, in light of these considerations.

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. (Of note, the best-case scenario for eteplirsen is the production of an abnormal Becker-type dystrophin, not normal dystrophin, but that will be discussed later.)

The second part of factor 3 is whether an effect has been demonstrated, and the standard remains ‘substantial evidence’ based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05.¹

¹ In some situations, FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness. See: “Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;” May, 1998.

The third part of factor 3, the determination that the demonstrated effect is “reasonably likely” to predict clinical benefit, is a matter of judgment. Thus, once there is substantial evidence of a treatment effect, the determination of whether the effect size is “reasonably likely” to predict clinical benefit is an area where flexibility can be applied. Presumably there is some threshold effect that would have to be achieved in order to satisfy this criterion, but this is not described in the regulations.

Is There a Basis for Accelerated Approval: Production of Dystrophin Protein in Skeletal Muscle?

The applicant assessed skipping of the messenger RNA exon using reverse transcriptase polymerase chain reaction (RT-PCR), a standard laboratory technique to detect RNA expression. Exon 51 skipping was confirmed by RT-PCR analysis in all patients treated with eteplirsen, establishing proof of concept that eteplirsen can cause at least some degree of exon 51 skipping, as intended. Because PCR is a highly sensitive technique that can detect even a few copies of messenger RNA, the findings do not support efficacy.

Dystrophin production was assessed by two widely-used and complementary methods: immunofluorescence (immunohistochemistry) and Western blot. Immunofluorescence is generally used to assess the presence or absence of proteins in tissue sections, and is particularly useful for cellular localization of protein (by light microscopy). Western blot provides quantitative analysis of protein, but no information on cellular localization.

Originally, the applicant evaluated the effect of eteplirsen on dystrophin expression in Studies 28, 33, and 201/202.

Of note however, as the May 26, 2016 goal date was approaching, the Office of New Drugs (OND) and the Center for Drug Evaluation and Research (CDER) could not reach agreement on the regulatory action for this NDA: the Office of New Drugs favored issuance of a complete response whereas CDER favored approval.

Thus, in order to obtain definitive data on dystrophin production to support accelerated approval, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in the ongoing Study 301 (PROMOVI). The applicant was told by CDER that if they were “...successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval...” Thus, data from Study 301 were included in this NDA and discussed below.

A. Immunohistochemistry

The applicant used immunohistochemistry in cross-sections of skeletal muscle biopsies to distinguish and count “dystrophin-positive” and “dystrophin-negative” muscle fibers. The methods are described in detail in Dr. Breder’s review. Briefly, following immunostaining of tissue sections for dystrophin, 4 fields were manually selected from the 4 quadrants of each slide, and images were captured (digitized) at 20X magnification. The contrast of each image was manipulated to enhance background staining so that most of the muscle fibers became visible, making it possible for the reader to perform a manual count of the total number of fibers. Image contrast was returned to normal, and positive fibers – fibers with at least some degree of

positive staining – were manually counted. For each field, the number of positive fibers was divided by the total number of fibers to calculate the percentage of positive fibers. Various rules were prospectively established to define “positive” fibers; in essence, a fiber could be classified as “positive” if its staining intensity was only slightly perceptible over background. Importantly therefore, a reading of 50% “positive” fibers in a tissue field is not tantamount to 50% (normal) dystrophin. A 50% figure means only that half the fibers exhibited staining that was at least barely perceptible over background.

Immunofluorescence data were also analyzed using Bioquant software. For these analyses, the user determined a brightness threshold for each digitized image, in essence selecting all pixels where staining intensity exceeded a particular user-selected value. Once selected, the software calculated the mean intensity of the selected pixels. Given that the region of interest for these analyses was limited to the pixels that exceeded a threshold rather than the total image, I do not consider the Bioquant analyses to be readily interpretable.

Study 33 was a 7-patient, exploratory, phase 1 study, initiated in 2007 at the Hammersmith and Saint Mary’s Hospitals, London, UK. Two subjects received a single 0.09-mg dose of eteplirsen in the extensor digitorum brevis (EDB) muscle of one foot and placebo in the contralateral foot. Five subjects received a single 0.9-mg dose of eteplirsen in the EDB muscle of one foot and placebo in the contralateral foot. After 14 to 28 days, dystrophin was detected adjacent to the needle tracks by immunohistochemistry and Western blot. Western blot analyses were not carried out for control muscles injected with placebo.

Study 28 was a 19-patient, exploratory, phase 1 study, initiated in 2009 at 2 sites in the UK. Patients had DMD amenable to exon 51 skipping. Eteplirsen was administered weekly by the intravenous route for 12 weeks at doses ranging from 0.5 to 20 mg/kg. There were up to 4 patients per dose level. After FDA expressed concerns about the reliability of the procedures and methods, the applicant responded that “Study 28 was an exploratory phase 1b study which was only intended to generate proof of concept data to guide future studies. For this reason, quality controls for the dystrophin data in Study 28 were not properly optimized.” Some data were missing, and after considering all of this information, the review team did not deem the results to be interpretable.

Study 201 was a single-center, double-blind, placebo-controlled, parallel-dose study in 12 patients with DMD. The study was initiated in 2011. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. The extension trial is well described in other reviews.

The 1^o endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry. The main comparison was planned to be the 50 mg/kg/week group at Week 12 and the 30 mg/kg/week group at Week 24 to the combined placebo group. The applicant’s original results are shown in Table 2, adapted from their clinical study report. As will be noted below, these results are not deemed to be reliable.

Table 2: Adapted From Table 11-1 of Applicant’s Clinical Study Report: Effect of Eteplirsen on Dystrophin-Positive Fibers Detected by Immunohistochemistry with MANDYS106

Time point		Placebo N = 4	30 mg/kg/wk Eteplirsen N = 4	50 mg/kg/wk Eteplirsen N = 4
Baseline	Mean	15.64	18.19	11.00
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment^b	Mean	11.59	41.14	11.79
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95 ^c	0.79
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4

It should be stressed again that the figures in the table represent the percentage of dystrophin-positive fibers, but in no way correspond to the percentage or quantity of dystrophin relative to a normal individual. Muscle fibers displaying virtually any staining intensity above background were considered “positive.” As noted above, therefore, a reading of 50% positive fibers means only that 50% of fibers exhibited staining that was perceptively above background.

These results were substantially reported in a 2013 publication,² which claimed that eteplirsen markedly increased functional dystrophin production: “...the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

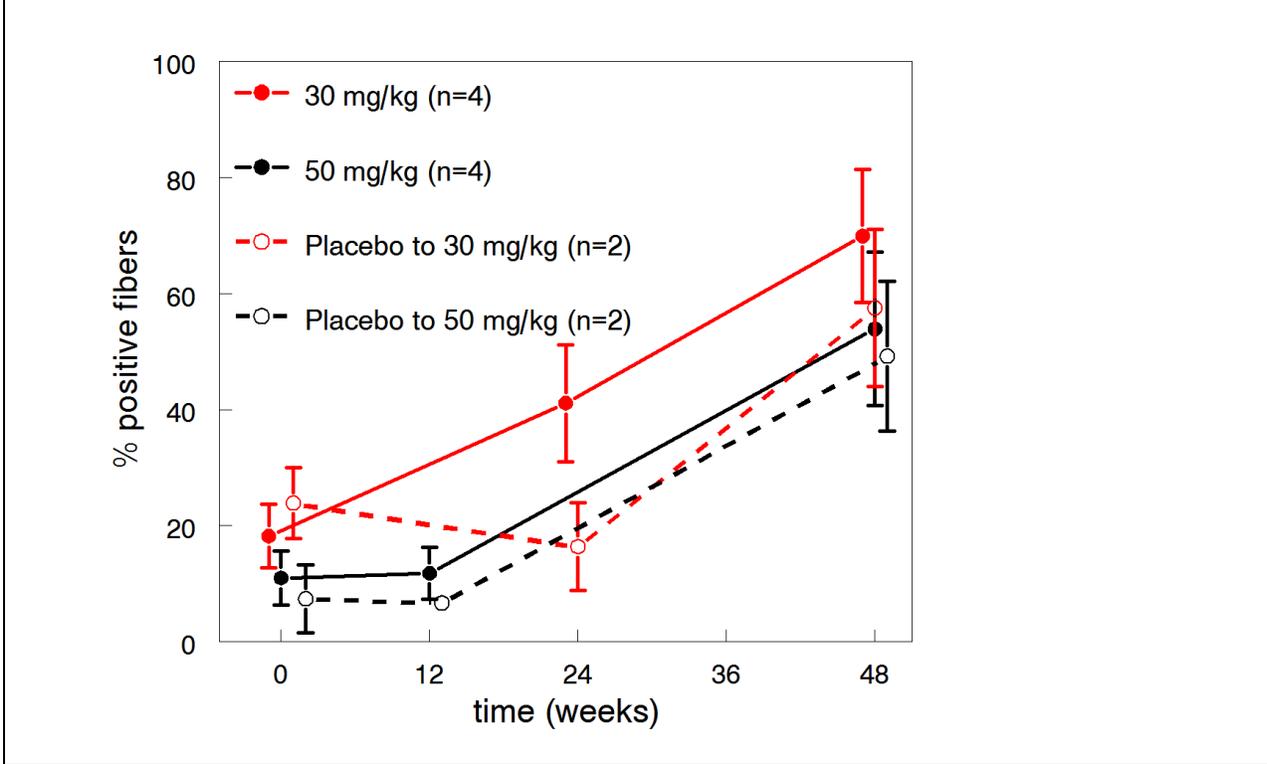
Publication of this paper was followed by a Sarepta press release,³ which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community. It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible (see below).

² Mendell JR, et al: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47

³ Sarepta press release, 8/8/13, at <http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1846052> [downloaded 5/10/16]

The original data from Nationwide Children’s Hospital submitted to FDA are plotted in Figure 2. Immunostaining for dystrophin appears to increase markedly in all 4 groups with time, with some 50 to 60% of fibers staining positive for dystrophin at 48 weeks. For reasons explained below, the review team disagrees with the veracity of these data.

Figure 2: Original Results of Dystrophin Immunostaining Using MANDYS106 Antibody: Percent Positive Fibers as a Function of Time – Results Not Verified on Re-read



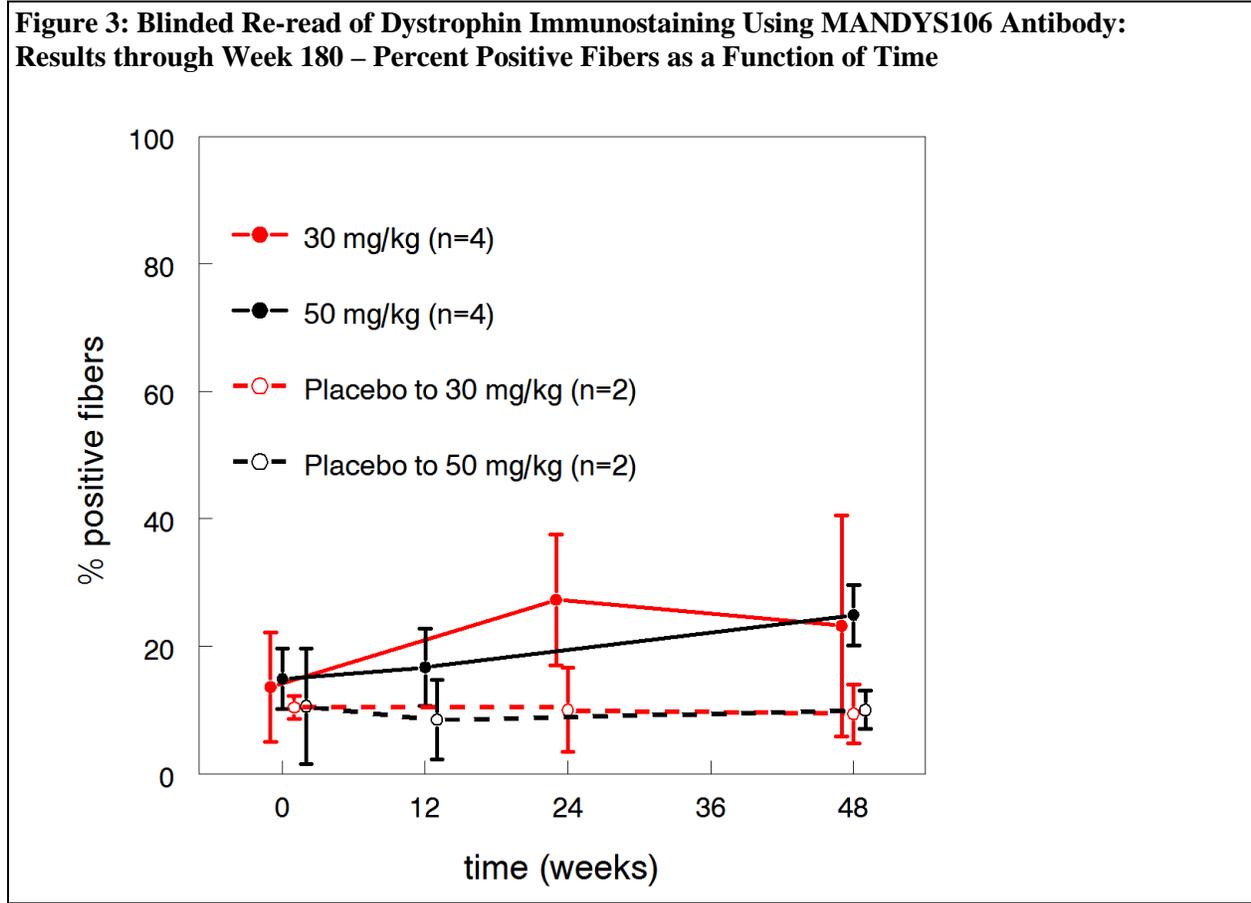
I was part of an inspection team that conducted (May 29 and 30, 2014) a site visit to Nationwide Children’s Hospital in Columbus, OH, where Study 201 was conducted. We found the analytical procedures to be typical of an academic research center, seemingly appropriate for what was simply an exploratory phase 1/2 study, but not suitable for an adequate and well controlled study aimed to serve as the basis for a regulatory action. The procedures and controls that one would expect to see in support of a phase 3 registrational trial were not in evidence.

Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had been read by a single technician using an older liquid crystal display (LCD) computer monitor in a windowed room where lighting was not controlled. (The technician had to suspend reading around mid-day, when brighter light began to fill the room and reading became impossible.) These issues are well described in a summary of inspectional findings in Dr. Breder’s clinical review (page 27). There was also concern that the reader, although masked to treatment assignment, was not masked to sequence/time (see below). Importantly, in a trial where all patients eventually received the active drug, knowledge of sequence could lead to the false appearance of a treatment effect, i.e., the appearance of increasing dystrophin expression

with time, simply by having a lower threshold for calling fibers “positive” at later time points in the study.

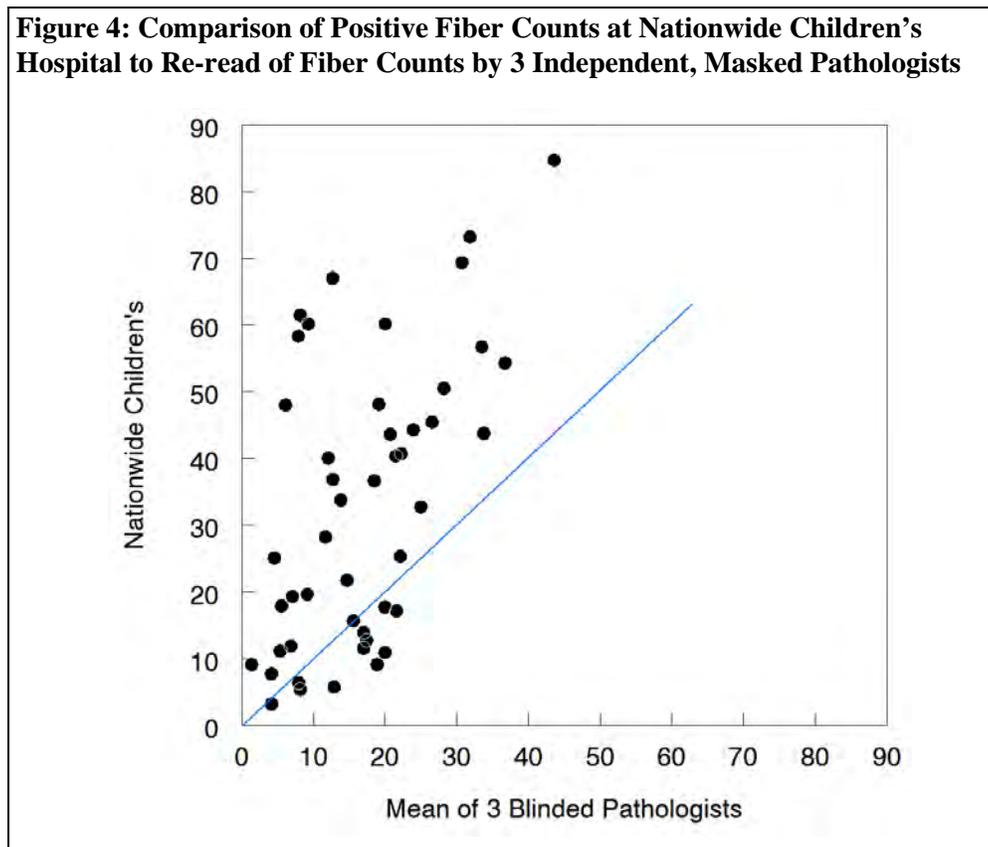
Having uncovered numerous technical and operational shortcomings in Columbus, our team worked collaboratively with the applicant to develop improved methods for a reassessment of the stored images. We suggested a re-read of all images by 3 independent masked readers, such that blinding could be assured and inter- and intra-observer variability could be characterized. We also suggested the use of better equipment, specifically, high-quality light-emitting diode (LED) computer monitors, in darkened rooms.

The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen at Week 24 (dashed red and black lines), there was no response between Weeks 24 and 48.



This re-analysis, along with the study published in 2013,² provides an instructive example of an investigation with extraordinary results that could not be verified. The publication, now known to be misleading, should probably be retracted by its authors.

Figure 4 shows the correlation between the dystrophin immunohistochemistry data as read by the technician at Nationwide Children’s Hospital and the 3 blinded pathologists. Each point represents data from a single patient at a single time point (an analysis of 24 images), as read by Nationwide Children’s Hospital (y-axis) and the group of 3 blinded pathologists (x-axis). Readings from the 3 pathologists are averaged. Perfectly correlated readings would lie along the blue line of unity. In most cases, the reading from Nationwide exceeds the reading from the pathologists, i.e., above and to the left. Thus, despite less-than-optimal lighting conditions that should have favored reduced reading of positive fiber counts at Nationwide Children’s Hospital, there was a striking tendency for the reporting of higher counts at that institution.

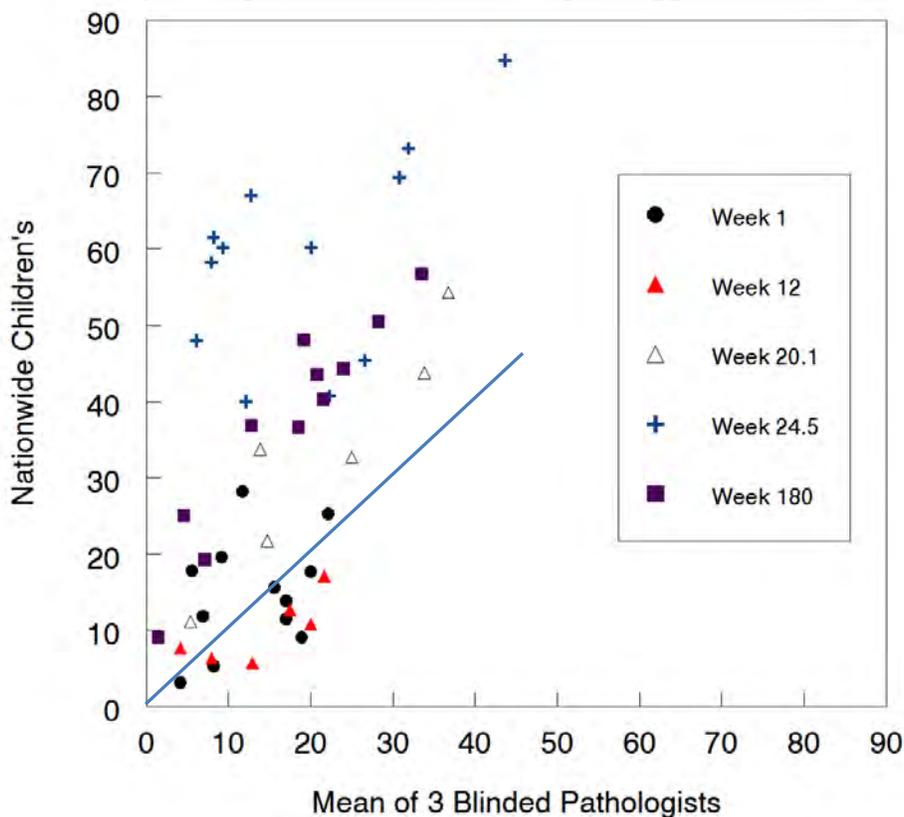


One might reasonably ask why the original readings were not reproduced by a blinded re-read. Figure 5 shows the same scatterplot between readings by Nationwide Children’s Hospital and the 3 blinded pathologists. In this display, however, readings from samples obtained at the disparate time points are shown with unique markers.

It is striking that the deviations between the readings of Nationwide and the re-read by the blinded pathologists differ substantially by study time point. Thus, at Week 1 (●) and Week 12 (▲), time points before increased dystrophin production would be expected, there is reasonable agreement between Nationwide and the pathologists, i.e., the points lie close to the blue line. In contrast, for the Week 24.5 time point (+), readings from Nationwide Children’s Hospital are much higher than those of the 3 pathologists, suggesting that blinding to sequence (i.e., time

point) was not achieved. At the time the Week 180 samples were read at Nationwide Children's Hospital, the technician was aware that the images would be re-read by 3 pathologists, which could explain why there is less exaggeration (i.e., the Week 180 readings are closer to the blue line of unity than the Week 24.5 readings).

Figure 5: Comparison of Positive Fiber Counts at Nationwide Children's Hospital to Re-read of Fiber Counts by 3 Independent, Masked Pathologists: Apparent Interaction with Time



Week 180 Data

As noted by the review team, the extension phase of the study (Study 202) has continued through the present. Eleven (11) of the 12 patients consented to undergo a fourth skeletal muscle biopsy at Week 180 (3.5 years), and these samples were analyzed using immunohistochemistry.

Prior to the analysis of the Week 180 samples, however, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Their aim was to compare the Week 180 dystrophin level to baseline for each patient. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these with samples from 6 untreated external DMD patients, all to be compared to the Study 201/202 patients at Week 180. Images were read by the same 3 pathologists, masked to treatment group.

For this analyses, the applicant claims a remarkable increase in dystrophin staining: the 9 baseline samples (including samples from 3 patients in Study 201/202 and 6 external controls) showed a mean percent positive fiber count of $1.1 \pm 1.3\%$ (mean \pm SD), whereas the Week 180 samples showed a mean percent positive fiber count of $17.4 \pm 10.0\%$. I will note that FDA made no attempt to inspect or oversee the new immunohistochemistry methods.

Given that the original baseline percent positive fiber count for patients from Study 201/202 was $13.0 \pm 6.2\%$, it would be important to understand why the results from a new immunohistochemistry protocol provided results more than an order of magnitude lower ($1.1 \pm 1.3\%$).

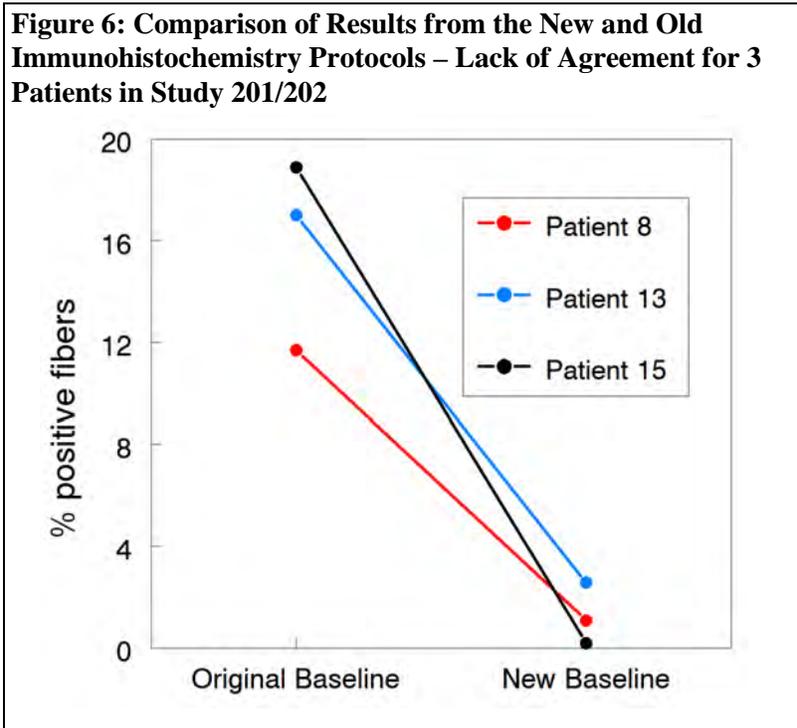
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue for separate immunohistochemistry analyses using both the old and new methods. Figure 6 shows how the two methods compare. These are essentially replicate analyses of a single tissue sample using the two methods.

There is an inexplicable difference of more than an order of magnitude between results using the new and old immunohistochemistry protocols. These marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

Commentary:

The review team provided much thoughtful discussion regarding the relative merit of immunohistochemistry for the quantitative assessment of dystrophin in skeletal muscle. My view is that such analyses, if properly blinded and controlled, can yield semi-quantitative information that could show differences in dystrophin production, e.g., 50% is more than 25%, although the method does not allow correlation of particular values of "percent positive" fiber counts with quantitative measures of muscle protein. Moreover, comparisons of fiber counts across centers, across experiments, or, for that matter, across staining or reading runs within a single laboratory, do not seem likely to be informative.



Recognizing that Study 201/202 was a small exploratory phase 1/2 study that was not powered to show a small change in dystrophin, the study provides no evidence of increased dystrophin production by immunohistochemistry.

It is unfortunate that the original readings from Nationwide Children's Hospital, purporting to show a marked effect of eteplirsen on dystrophin-positive fiber counts – counts now known to be unreliable – led to the perception that the drug produces large amounts of dystrophin. These results fueled the public perception that eteplirsen is highly effective as well as the DMD community's reluctance to participate in placebo-controlled trials. Only recently, an unauthored report in the Wall Street Journal stated: "The trial turned up evidence that eteplirsen makes good on pumping out dystrophin, a feat no treatment has managed."⁴ Presumably this misperception has been carried over from the initial 2013 reports.

B. Western blot

1) Data analyzed prior to the PDUFA goal date

A second, more important line of evidence regarding dystrophin production is Western blot, a standard, widely-used, analytical technique to assess levels of protein in biological tissues. Western blot was used to quantify dystrophin protein directly, and the methods are described by others.

For a variety of reasons discussed by Dr. Rao, the Western blot analyses originally conducted by the applicant were technically unsatisfactory. The Western blots from the first 3 time points had oversaturated bands, lacked appropriate controls, and were essentially uninterpretable. After conducting a site visit to the Columbus OH laboratory, FDA rendered advice to the applicant with the goal of improving technical aspects of the assay for future use.

The applicant amended the study protocol to allow for an additional skeletal muscle biopsy at Week 180 (3.5 years), potentially enabling pre- to post-treatment comparisons of Becker-type dystrophin after prolonged eteplirsen treatment. As noted above, 11 of the 12 patients in Study 201/202 consented to undergo a fourth skeletal muscle biopsy at Week 180. Of note, the baseline samples had been obtained from biceps muscle, whereas the Week 180 samples were obtained from deltoid muscle.

Two blocks were prepared from each patient sample. Sections from both blocks were pooled during homogenization for lysate preparation, and Western blots were run in duplicate.

The individual (anonymized) values for the Western blot analysis are shown in Table 3. As reported by the review team, the analysis for 11 of the 12 original patients showed a mean dystrophin value of 0.93% ± 0.84% of normal (mean ± standard deviation) after 3 to 3.5 years of eteplirsen treatment (3 years in patients initially randomized to placebo; 3.5 years in the other patients). Mean values were virtually the same for the lower (30 mg/kg/week) and higher (50 mg/kg/week) dose groups; there is no suggestion of a dose-response.

⁴ A Legal Test for the FDA: Black letter law dictates approval for a muscular dystrophy drug; Wall Street Journal, May 9, 2016.

Of note, the Western blot values are quite variable, both between patients and between duplicate runs *within* patients (i.e., repeatability; intra-assay precision), Table 3.

Mean values ranged from a maximum of 2.47% in Patient J, to near-zero in Patient H, and to zero in 2 patients (E and G). For some patients, there were considerable discrepancies between duplicate runs (the intra-assay difference was >0.5% in Patients B, C, D, and J). Aside from patients with zero or near-zero dystrophin, only 3 patients showed reasonable intra-assay agreement: Patients F, L, and K.

Given that these numbers represent duplicate runs from tissue homogenates, intra-assay differences suggest limited precision/reproducibility of the method, heterogeneity of the samples, or both.

Table 3: Individual Week 180 Western Blot Analyses – Study 201/202

Subject	Dose	Western blot				Group Mean ± SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)	
L	30 mg/kg	0.58	0.46	0.52	0.52	
K	30 mg/kg	1.45	1.78	1.62	1.62	
J	30 mg/kg	2.83	2.11	2.47	2.47	
H	30 mg/kg	0.02*	0.28	0.15	0.14	
G	Placebo to 30 mg/kg	0.17*	0.15*	0.16	0	
F	Placebo to 30 mg/kg	0.93	1.02	0.98	0.98	0.96 ± 0.95
E	50 mg/kg	0.19*	0.16*	0.18	0	
D	50 mg/kg	0.75	0.24*	0.50	0.38	
C	50 mg/kg	1.22	0.69	0.96	0.96	
B	50 mg/kg	2.43	1.67	2.05	2.05	
A	Placebo to 50 mg/kg		1.15	1.15	1.15	0.91 ± 0.79

* below limit of quantitation

Change in Dystrophin with Treatment:

The critical question, of course, is whether the value of 0.93% is meaningfully greater than the value at baseline, or even meaningfully greater than zero. Assuming that one considers this value greater than zero, the baseline pre-treatment levels of dystrophin in these 11 patients are critical in determining whether eteplirsen was responsible for the dystrophin detected at Week 180.

Unfortunately, adequate pre-treatment tissue samples were available for only 3 of these 11 patients. Thus, the applicant supplemented these data with muscle biopsies from 6 untreated patients with DMD amenable to exon 51 skipping who were external to the study.

Whereas the Week 180 samples were obtained from deltoid muscle, 8 of 9 of the controls were obtained from biceps muscle (the other one was obtained from deltoid). As noted above, the non-clinical review team found "...wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is

warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients.” Use of disparate muscle groups between patients in Study 201/202 and controls was, obviously, ill advised. The finding of a difference between patients in Study 201/202 and the external controls could simply represent a difference between muscles.

FDA’s advice to the applicant (March 30, 2015) is still germane: "The control biopsy tissue that you propose to use is from a number of different muscle groups, such that differences that may exist in dystrophin expression among muscle groups may affect your results. However, in the context of other major sources of variability among biopsies (including both intra- and inter-individual differences even within the same muscle group), it appears reasonable for you to proceed with these controls, with the understanding that dystrophin changes would need to be robust to be interpretable as a drug effect."

Averaging Western blot data from pre-treatment biopsies of the 2 patients from Study 201/201 and the external treatment-naïve patients, the applicant reported a baseline dystrophin value of 0.08% ± 0.13% (mean ± standard deviation). Obviously, all but 2 of these controls are external, such that the comparison to the treated patients in Study 201/202 is non-randomized and indirect.

Table 4: Individual Untreated DMD Control Samples, Western Blot Analysis (% Normal Dystrophin)

Study; Subject	Dose	Western blot				Group Mean ± SD	All Mean ± SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)		
201/202; X	0	0.05*	0.07*	0.06*	0	0 ± 0	0.08 ± 0.13
201/202; A	0	0.19*	0.08*	0.14*	0		
201/202; B	0	0.13*	0.07*	0.10*	0		
external; A	0	0.12*	0.14*	0.13*	0	0.12 ± 0.15	
external; B	0	0.03*	0.12*	0.08*	0		
external; C	0	0.37	failed	0.37	0.37		
external; D	0	0.04*	0.30	0.17*	0.15		
external; E	0	0.20*	failed	0.20*	0		
external; F	0	0.40	0.09*	0.25*	0.20		

* below limit of quantitation

In determining whether there is substantial evidence that eteplirsen produced dystrophin in the patients in Study 201/202, the critical questions are whether these values, near the lower limit of quantification of the assay, are actually interpretable, and whether the comparison between these subjects and a predominantly external group of untreated patients is valid.

The review team has pointed out important limitations with respect to comparability of the Western blot results from the untreated controls, summarized below:

- Biopsies from controls were obtained from biceps, whereas Week 180 biopsies from eteplirsen-treated patients were obtained from deltoid. There is some evidence that dystrophin concentrations differ by muscle group, and the study does not account for this possibility. Because the study is not well controlled, the difference between these groups of patients cannot be attributed to a drug effect.
- Two-thirds (6 of 9) of the control patients were from Study 301, and were external to study 201/202. There is no way to know how these particular patients were selected for the purpose of this comparison.
- Degradation of dystrophin or loss of immunoreactivity might occur during prolonged storage of tissue samples. If so, it could have affected the baseline samples from the 3 patients in Study 201/202, which were frozen for over 3 years prior to analysis. Note that the data are consistent with loss in immunoreactivity over time (Table 4). The per-protocol values for all 3 patients from Study 201/202 whose samples were stored for 3 years are 0 (top), whereas 3 of 6 of the samples from the external controls (bottom) are greater than zero. Although the numbers of samples are small and the comparison is non-randomized, the data nevertheless support the concept that immunoreactive dystrophin decreases during storage.

For these reasons, the review team questioned the comparability of these two groups of patients, and I agree. Having compared samples from different muscle groups in independent groups of patients, the study was not adequate and well controlled; therefore, the validity of the comparison is uncertain. The data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Having heard arguments and opinions from both the applicant and the review team, the Advisory Committee, despite extraordinary public activism and pressure to vote favorably, voted 7 to 6 that the applicant had 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. Moreover, 2 of the Committee members who voted “yes” were patient representatives.

Correlation between the applicant’s two methods to assess dystrophin

The discussion of the Week 180 dystrophin analyses would not be complete without a comparison of the results of the two complementary methods used by the applicant. Of note, the improved immunohistochemistry analyses and Western blot analyses were performed on *the same blocks of tissue*, and one should expect a reasonable correlation between the two methods if in fact the data are reliable.

Of note, there is a striking lack of correlation between these two methods of dystrophin assessment (Figure 7). It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, whether the Western blot methods are inaccurate, or whether both methods are inaccurate. My view is that it is not possible to render a positive regulatory decision on the basis of unreliable data from these 11 patients. Internal consistency is lacking.

2) Data analyzed after the PDUFA goal date

As noted above, as the May 26, 2016 goal date was approaching, OND and CDER could not reach agreement on the regulatory action for this NDA.

In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301 [PROMOVI]). These samples were originally planned to be analyzed at the end of the study;

however, we requested an interim analyses of a subset of samples. As described by Drs. Rao, Farkas, and Bastings, Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples had been obtained at baseline (prior to treatment) and at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

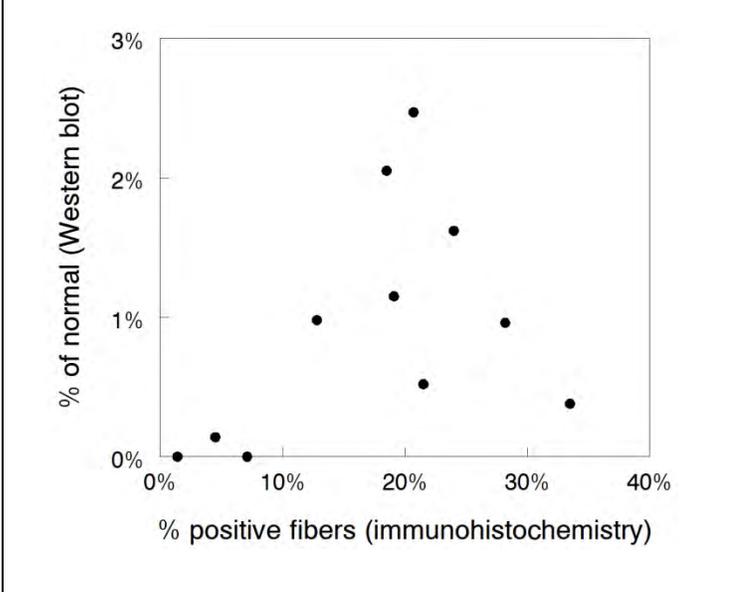
The age of these 13 patients ranged from 7 to 13 years. Paired pre- and post-treatment samples were run in side-by-side lanes on the gels, and each gel was run in duplicate. A muscle sample from a healthy 14 year-old boy with no pathologic diagnosis served as the reference sample; values from the DMD patients were reported as percent of normal.

Dr. Ashutosh Rao from the Office of Biotechnology Products reviewed the methodology and the technical reliability of the Western blot assay. Dr. Rao also conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) as the analyses were being run. Xiang Ling, Ph.D., from the Office of Biostatistics, performed the statistical review on the data.

According to the protocol, acceptance of the result from each gel was contingent on two factors: 1) the R^2 value for the linearity of the standard curve of the normal control had to be > 0.9 ; and 2) the dystrophin band for the negative control DMD sample on the gel had to have a density lower than the lowest sample of the standard curve (0.25%). Samples that did not meet both criteria were deemed 'failed' and were not considered in the analyses. As it turned out, 22 of the 52 gels (42%) failed, such that many of the values represent single readings rather than the average of two. There was one patient for whom none of the values met acceptance criteria. Thus, the applicant reported pre- and post-treatment data for 12 of the 13 patients.

The applicant used 3 methods to consider values below the 0.25% lower limit of quantification: 1) consider such values to be zero; 2) analyze such values as actually reported; and 3) consider such values to be 0.24%.

Figure 7: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



The review team believes the most appropriate analysis is the second: analysis of all values as reported, but the results were similar for all 3 methods.

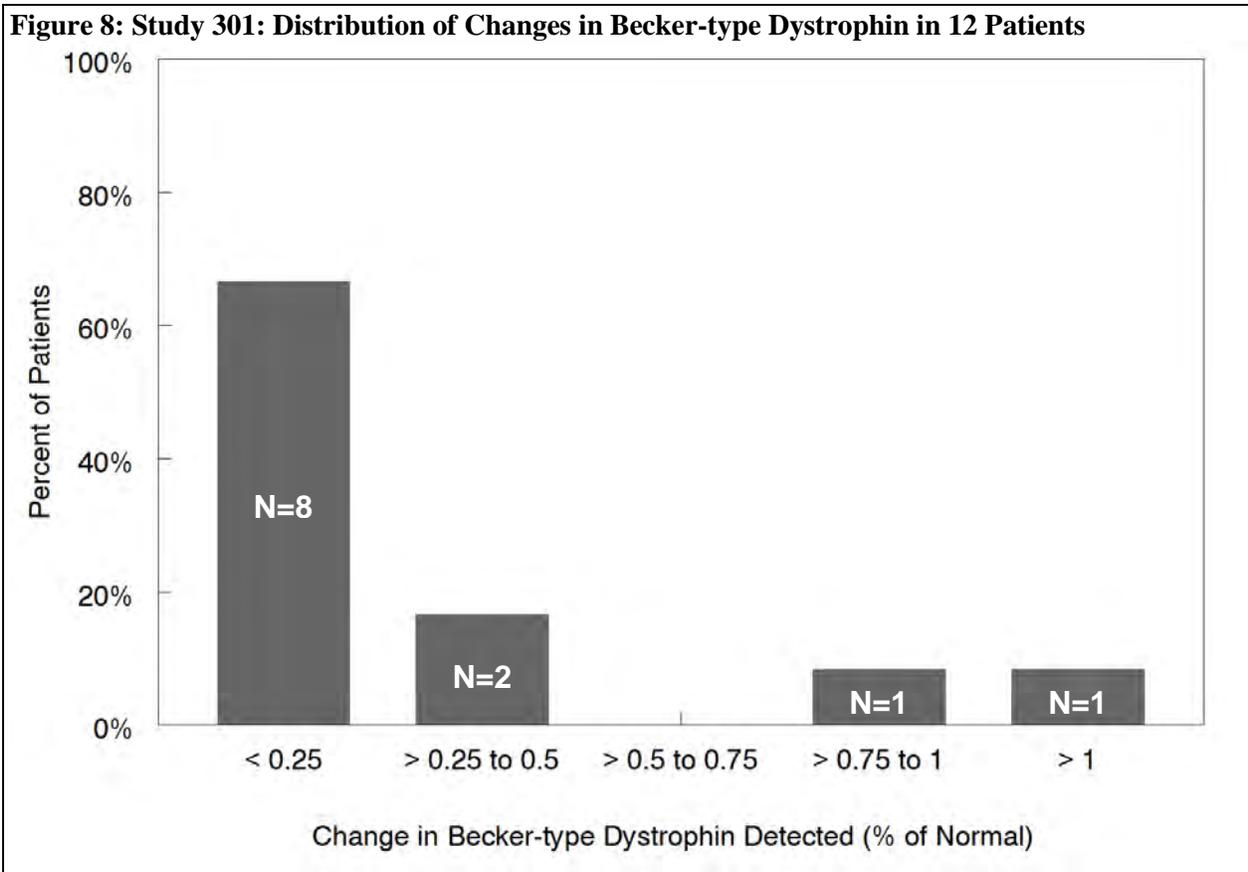
Reporting values below the limit of quantification as 0, pre- and post-treatment values are $0.06\% \pm 0.14\%$ and $0.38\% \pm 0.50\%$, respectively (mean \pm standard deviation), $p < 0.05$. For the 'as reported' analysis, pre- and post-treatment values are $0.16\% \pm 0.12\%$ and $0.44\% \pm 0.43\%$, respectively, $p < 0.05$. Reporting all values below the limit of quantification as 0.24%, pre- and post-treatment values are $0.26\% \pm 0.05\%$ and $0.48\% \pm 0.41\%$, respectively, $p < 0.05$. Individual data for the 'as reported' analysis are shown in Table 5, adapted from listing 1.1 of the applicant's "Preliminary Report: Western Blot Interim Analysis of Novel Dystrophin Expression in Muscle Biopsy Samples from Week 48 of the Clinical Study 4658-301," submitted June 27, 2016.

Irrespective of the method used to express data below the limit of quantification, the mean change is similar, ranging from 0.22% to 0.32% of normal, a treatment effect of approximately 2 to 3 parts per thousand.

Table 5: Study 301: Pre- and Post-treatment Values of Becker-Type Dystrophin

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.24	1.33
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08	1.57	
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	0.11	0.01
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17	0.12	
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.05	0.43
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12	0.47	
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.02	0.07
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31	0.09	
		fail	0.19					fail	0.01		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.03
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09	0.21	
		pass	1.02					fail	0.21		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34	0.21	
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25	7	Baseline	fail	0.04	0.17	0.25
		pass	0.17					pass	0.17		
	Week 48	fail	0.22	0.42			Week 48	fail	0.22	0.42	
		pass	0.42					pass	0.42		

The distribution of these changes is shown graphically in Figure 8. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a treatment effect greater than 1%.



Commentary: Study 301 was a baseline-controlled study, where each patient served as his own control: pre- and post-treatment biopsies were obtained from the same muscle and Western blot analyses were run concurrently. An FDA inspection team observed the performance of the assays and considers the results to be reliable. Thus, unlike the data obtained from Study 201/202, the Study 301 data are considered by the review team to have been generated from an adequate and well controlled study. Study 301 provides substantial evidence of an effect of the surrogate endpoint – Becker-type dystrophin.

The critical question is whether the quantity of dystrophin produced here – a mean of 2 to 3 parts per thousand – is reasonably likely to predict clinical benefit.

With levels of Becker-type dystrophin higher in Study 201/202 (at Week 180) than in Study 301 (at Week 48), the applicant speculates that there is greater dystrophin accumulation with longer durations of treatment. These differences, however, could also be due to cross-laboratory methodological differences or play of chance; therefore, such an interpretation is highly speculative.

The Question of “Reasonably Likely to Predict Clinical Benefit”

As discussed above, the accelerated approval of eteplirsen hinges on: 1) whether Becker-type dystrophin is an appropriate surrogate endpoint for the disease; 2) whether there is substantial evidence that eteplirsen produces Becker-type dystrophin in skeletal muscle, and 3) whether such dystrophin produced is reasonably likely to predict clinical benefit, i.e., whether it is functional, and whether the quantity produced is adequate.

1. Is dystrophin an appropriate surrogate endpoint for Duchenne muscular dystrophy?

The review team believes that dystrophin is on the causal pathway of the disease, and there is no debate about the appropriateness of dystrophin as a surrogate endpoint for Duchenne muscular dystrophy.

2. Is there substantial evidence that eteplirsen produces dystrophin in skeletal muscle?

Prior to receiving the new Western blot data from Study 301 on June 27, 2016, the review team did not believe that substantial evidence from adequate and well controlled trials had been submitted to support an accelerated approval.

Study 201/202: Immunohistochemistry analyses were performed to assess and compare percent dystrophin-positive fibers at various time points before and during treatment. This is a standard technique that has been used by many laboratories for decades to assess dystrophin levels in DMD and Becker’s patients. Importantly, the analysis showed no evidence of dystrophin production through 48 weeks of treatment with eteplirsen. This information is particularly germane, because, unlike the Western blot analyses from Study 201/202, the immunohistochemistry analyses are adequately controlled. The lack of a positive finding from the blinded re-read of the immunohistochemistry data with proper controls undercuts the evidence of dystrophin production from Western blot analyses.

The applicant supplemented these data with new analyses from Week 180 that purport to show a remarkable increase in dystrophin from pre-treatment levels. Unfortunately, an altered immunostaining protocol was used, and there was an inexplicable difference of more than a log between results from the new and old protocols, rendering interpretation impossible.

The Western blot data from Study 201/202 were largely externally controlled, and there were questions with respect to the proper selection of control patients, differences in the specific muscles analyzed, and concerns regarding the possible degradation of immunoreactive dystrophin in tissue samples that might occur during long-term storage and lead to a false-positive result. Importantly, ignoring the baseline data and focusing only on the Week 180 samples, there is a striking lack of correlation between the immunohistochemistry data and the Western blot data, i.e., there is no internal consistency. Thus, these data provide no basis to believe that the study was adequate and well controlled.

Study 301: The new data submitted on June 27, 2016 were obtained from an adequate and well controlled study. This baseline-controlled study shows a statistically significant increase in Becker-type dystrophin with treatment, the surrogate endpoint. Thus, there are now data showing Becker-type dystrophin production, albeit at a small level, from one adequate and well controlled trial (Study 301), with inconclusive data from Study 201/202.

The question of “reasonably likely” is, therefore, an issue of the quantity of protein produced. As noted above, Study 301 showed a treatment effect of 2 to 3 parts per thousand in Becker-type dystrophin after 48 weeks. Study 201/202, although not adequate and well controlled, nevertheless suggested a treatment effect of 8 to 9 parts per thousand after 3.5 years.

3. Is the dystrophin that was produced reasonably likely to predict clinical benefit, i.e., is it functional, and is the quantity adequate?

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Function is therefore a matter of judgment for which regulatory flexibility can be extended. The review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as in the Becker form of the disease. Although there can be no certainty on this point, the uncertainty is small relative to the uncertainty regarding the adequacy of the quantity, and so function is less germane to the question of “reasonably likely.” In short, it is the *quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.*

It must be stated that the minimum level of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown. The raw data are shown in Figure 9, but this is an area where we must consider what is known about the disease and apply medical judgment.

There are two ways to consider the quantity of Becker-type dystrophin produced: as a binary responder analysis, and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

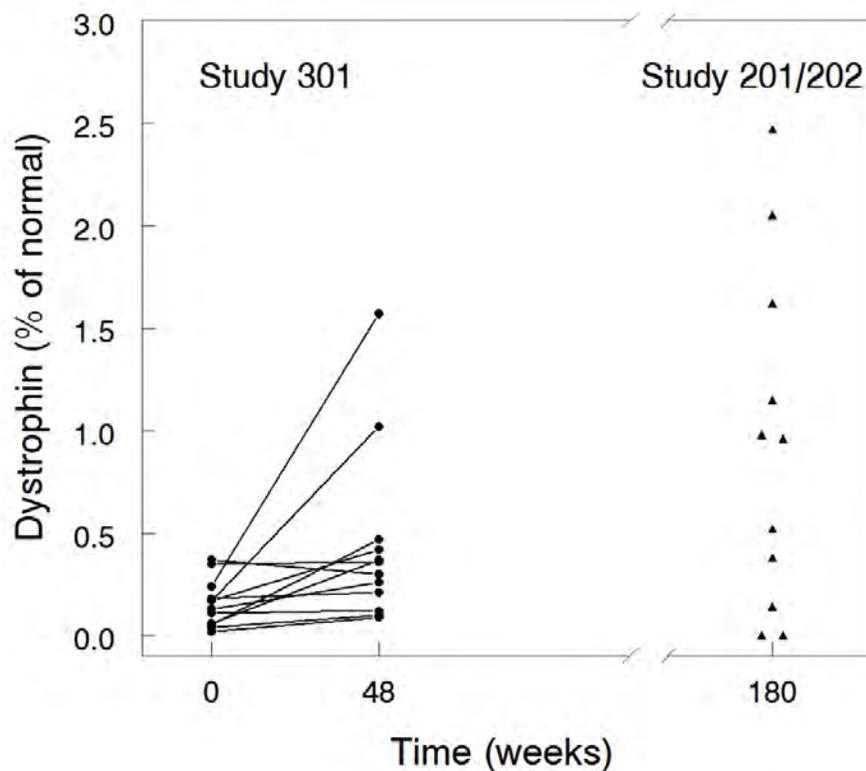
The problem with a responder analysis is that there is no rational basis upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Drs. Farkas and Bastings have tried to provide a framework to help put these small increases into perspective. The applicant’s data show that dystrophin levels in treatment-naïve DMD patients range from 0 to approximately 0.4% by Western blot; the applicant has not detected values > 0.4% in treatment-naïve patients.

DMD experts, including those involved with the development of eteplirsen, have stated that levels < 3% are generally associated with the typical DMD phenotype, and no patient has been found to have or produce a level of Becker-type dystrophin > 3% in response to treatment.

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have focused on publications from a number of laboratories that attempt to relate particular levels of dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Some have also cited non-clinical data to relate dystrophin levels to maintenance of physical function. It is important to recognize, however, that many methodological factors affect the results of these assays, and comparison of values across various laboratories could lead to erroneous conclusions.

Figure 9: Studies 301 and 201/202: Expression of Becker-type Dystrophin by Western Blot



Van den Bergen *et al* studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker muscular dystrophy (van den Bergen JC, et al. *J Neurol Neurosurg Psychiatry* 2014;85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their patients with dystrophin levels <10% showed low muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Chamberlain, who stated at the open public session at the advisory committee meeting that very low levels of dystrophin may be beneficial, discussed in a published paper (*Basic Appl Myol.* 7 [3&4]: 251, 1997) that “...a majority of fibers must accumulate approximately 20% of wild-type levels of dystrophin for a significant correction of the muscle pathology,” a view that seemingly contradicts the comments he made at the advisory committee meeting.

Anthony K *et al* (*Neurology* 2014;83:2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. Variability was particularly pronounced with low levels of dystrophin.

During their presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, stated:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: official transcript of the meeting; underlining for emphasis.)

It appears, therefore, that reproducibility of assays among academic centers has not been established, such that it would not be feasible to compare an increase in Becker-type dystrophin of 0.2 to 0.3% (or even far greater increases) with dystrophin values cited in the literature for other mutations/patient populations, assessed by other laboratories.

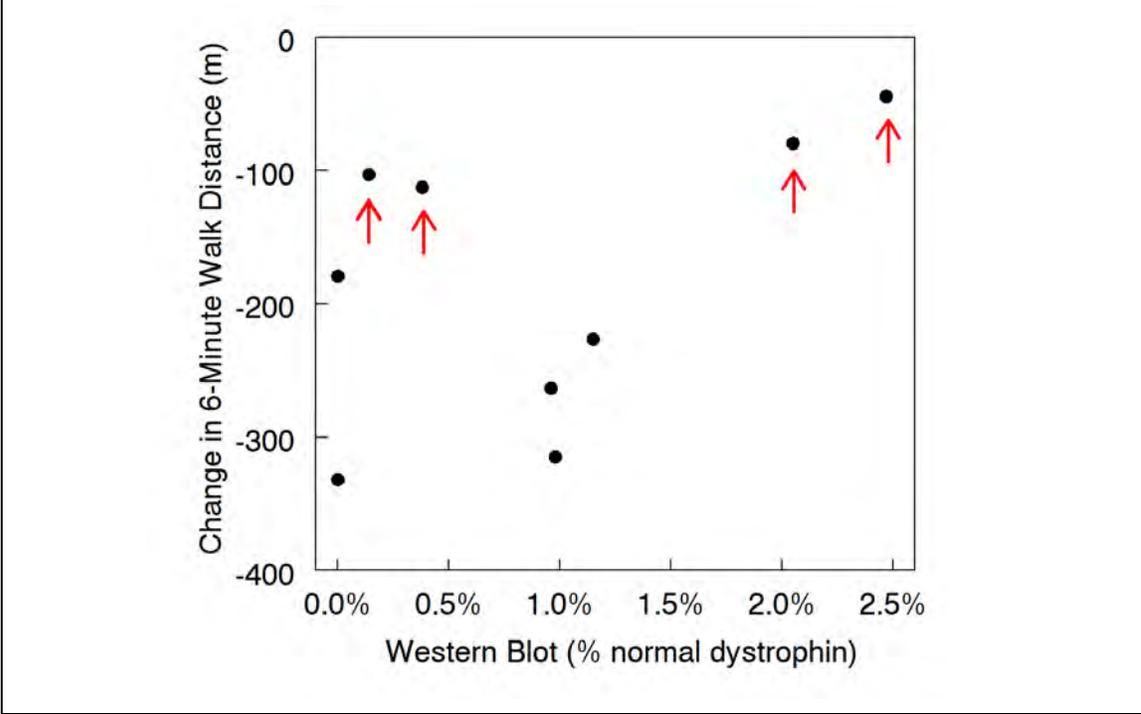
Do the clinical data bolster the question of “reasonably likely?”

The applicant collected data on both dystrophin production and physical performance in Study 201/202. Such data have the potential to support the concept that the dystrophin level predicts clinical response, and would support the ‘reasonably likely’ premise. Despite detailed testimonials from patients in Study 201/202 claiming improvements in clinical performance, the Division concluded, on the basis of the data presented in the NDA, that no patient in Study 201/202 clearly deviated from the natural history of the disease. They reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Dr. Bastings opines that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

Within Study 201/202, it is also reasonable to consider the correlation between the quantity of dystrophin detected and maintenance of physical function in individual patients. The presence of a correlation would help support the “reasonably likely” question.

For the 9 patients who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, Figure 10 shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years. For the 4 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study, but 2 had levels that were close to zero. Importantly, therefore, these data do not show a quantitative correlation between the surrogate endpoint deemed reasonably likely to predict clinical benefit, i.e., Becker-type dystrophin levels, and the clinical benefit, i.e., maintenance of walking velocity. In Dr. Bastings’ memorandum, he provides careful documentation of the trajectories of physical performance for each patient, comparing their changes in performance to the quantity of dystrophin detected. After careful consideration, he finds no correlation whatsoever.

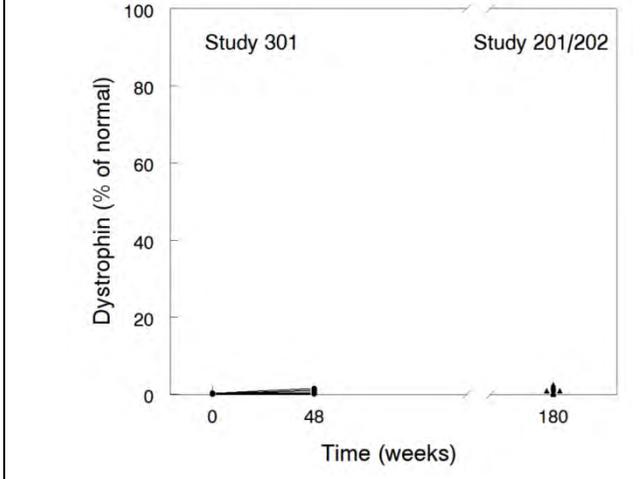
Figure 10: Study 201/202 – Lack of Correlation between Quantity of Dystrophin Detected and Preservation of Physical Function (6-Minute Walk Distance)



Although it should be obvious that changes on the order of a percent or two are small, it is nevertheless worthwhile to view these data at full scale to gain perspective (Figure 11). The figure is identical to Figure 9, except for the scale on the y-axis.

If dystrophin were simply an enzyme responsible for biochemical activity in myocytes, one could posit that a very small quantity of the protein could exert a substantial treatment effect, especially because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury from stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. Finally, we must recognize receiving a treatment that increases dystrophin by 0.3% is not that same as being born with 0.3% more dystrophin.

Figure 11: Studies 301 and 201/202: Expression of Becker-type Dystrophin by Western Blot (full scale)



3. Dose-response

Although the issue is somewhat peripheral to the “reasonably likely” question, the presence of a dose-response in Study 201/202 would have provided supportive evidence that the dystrophin that was detected was produced by eteplirsen. A dose-response was not evident, although one could reasonably argue that the trial was very small and that the difference between 30 and 50 mg/kg/week was unimportant.

In a monkey study conducted to assess the pharmacodynamic effects of eteplirsen, a 1-log increase in dose (from 4 to 40 mg/kg) caused minimal increase in exon 51 splicing as detected by PCR (Section 4, Table 1). However, with a 2-log increase in dose (from 4 to 320 mg/kg), there was a log increase in exon 51 splicing. As noted in Section 4 of this memorandum, it is possible that much higher doses of eteplirsen could have a substantially greater effect, which might translate to clinical benefit.

Advisory Committee

The Advisory Committee was asked to discuss: a) the strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients relative to their baseline, and b) the 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. (Of note, the data from Study 301 were not known/available to the Advisory Committee.)

Although the Committee failed to reach consensus on these questions, the discussion, summarized below, is of interest.

With respect to production of dystrophin, about half of the committee members found evidence that eteplirsen increased the amount of dystrophin produced in skeletal muscles. 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 (Figure 10), and one cited concerns about the lack of a dose-response (Table 3).

Only four Committee members had explicit comments with respect to the clinical meaningfulness of the amount of dystrophin detected in treated patients, and their opinions were split. One member 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 felt strongly 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 there is no basis to determine the quantity of dystrophin that 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 in the study, the amount was not clinically meaningful, based on the lack of correlation between dystrophin levels and clinical results (Figure 10).

The Committee voted on whether the applicant had 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.

Ultimately, 7 members voted “no” and 6 voted “yes,” after one member changed his vote from “no” to “yes.” In explaining their “no” votes, 5 committee members opined that the studies were not adequate and well controlled; they 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 6 “Yes” votes included the consumer representative and 2 patient representatives. These individuals 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. Two members who voted “No” stated that their vote was justified by the way the question was phrased, but that the patient testimonies suggested the drug works.

Is There a Basis for a Conventional Approval Based on Clinical Data?

The clinical data have been well described by the review team. The development program consisted of one trial (Study 201/202) with a relatively short (24-week) placebo-controlled portion (Study 201) followed by a long-term extension study (Study 202). Although the applicant submitted biopsy data from the ongoing Study 301, no clinical data have been submitted from that study.

As noted above, for Study 201, patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2) and followed for 4 additional weeks. The trial was extended to an open-label phase (Study 202), where all 12 patients continued to receive eteplirsen without interruption, although investigators and patients remained blinded to dose.

The 1° endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry, but there were numerous exploratory endpoints.

When the data from Study 201 were originally analyzed, the applicant found that eteplirsen caused a striking and unprecedented increase in dystrophin production, based on the reading of the immunohistochemistry data at Nationwide Children’s Hospital, with supportive data from Western blot analyses.

The clinical data, too, were interpreted as positive. As discussed by the review team, 2 patients in the 30 mg/kg/week treatment group became unable to ambulate soon after the trial began, and there were no significant differences in 6-minute walk distance among the groups. Despite clearly negative results, the applicant performed a *post hoc* analysis that omitted the 2 patients in the eteplirsen group who became unable to ambulate. They represented these results as positive, and publically promoted both the immunohistochemical dystrophin results and the 6-minute walk data as positive (see clinical review).

Although FDA would later determine that the analyses underlying these data were not valid, the publicity from the paper² and Sarepta’s press release³ raised unrealistic expectations of efficacy

in the DMD community. It was these perceptions that led the applicant to conclude that a second placebo-controlled study would not be feasible.

FDA strongly suggested a second, larger, adequately-powered, placebo-controlled trial, but the applicant was reluctant to run such a trial, in part because their supply of drug was limited, and in part because of their insistence that the DMD community would not agree to participate in a trial where there was a chance of receiving placebo. Faced with the applicant's unwillingness to conduct a second placebo-controlled trial, FDA agreed to an externally-controlled trial: a comparison between patients in the ongoing Study 202 and patients in an external control group. The Division expressed strong concern, however, with respect to the interpretability of such a trial with 6-minute walk distance as the endpoint, given that physical performance is not a "hard" endpoint, but can be influenced by motivation and other factors. Citing FDA Guidance,⁵ the Division noted that the treatment effect would have to be dramatic for the results from an externally-controlled study to be interpretable. Details of the interactions between FDA and Sarepta are well documented by the review team.

International guidelines, adopted by the FDA as guidance, stress caution with respect to the interpretation of data from externally-controlled trials. As noted in the International Conference on Harmonization (ICH) E10 Guideline,⁵ blinding and randomization, used to decrease bias in randomized controlled trials, are not utilized in externally-controlled trials; the inability to control bias is a critical limitation of externally controlled trials. Groups can be dissimilar with respect to a wide variety of factors that could influence outcome – factors that are both known and measurable as well as factors that are unknown. As explained by Dr. Robert Temple at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, it has been well documented that untreated historical-control groups tend to have worse outcomes than apparently similarly chosen control groups of randomized studies, possibly reflecting a selection bias.

The ICH E10 Guideline explains: "A consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials. The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." In essence, in order to be interpretable, the finding of a difference between groups should be large – so large that the difference is patently obvious without the need to rely on inferential statistics.

Having heard FDA's concerns regarding the potential difficulty in interpreting an externally-controlled trial, the applicant nevertheless obtained access to individual data from patients with DMD from Professor Eugenio Mercuri at the Catholic University in Rome on behalf of the Italian DMD Registry database (n=97) and from Professor Nathalie Goemans at the University Hospitals in Leuven (n=89). From these 186 patients, 50 had a genotype amenable to exon skipping therapy, were using corticosteroids at baseline, had 6-minute walk data available at baseline, and were ≥ 7 years old. Among these 50 patients, 13 had a genotype amenable to

⁵ Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001

exon 51 skipping therapy. I will note that the review team has been unable to gain an understanding of how dates of inception were determined for registry patients, i.e., when patients were considered to have ‘enrolled.’

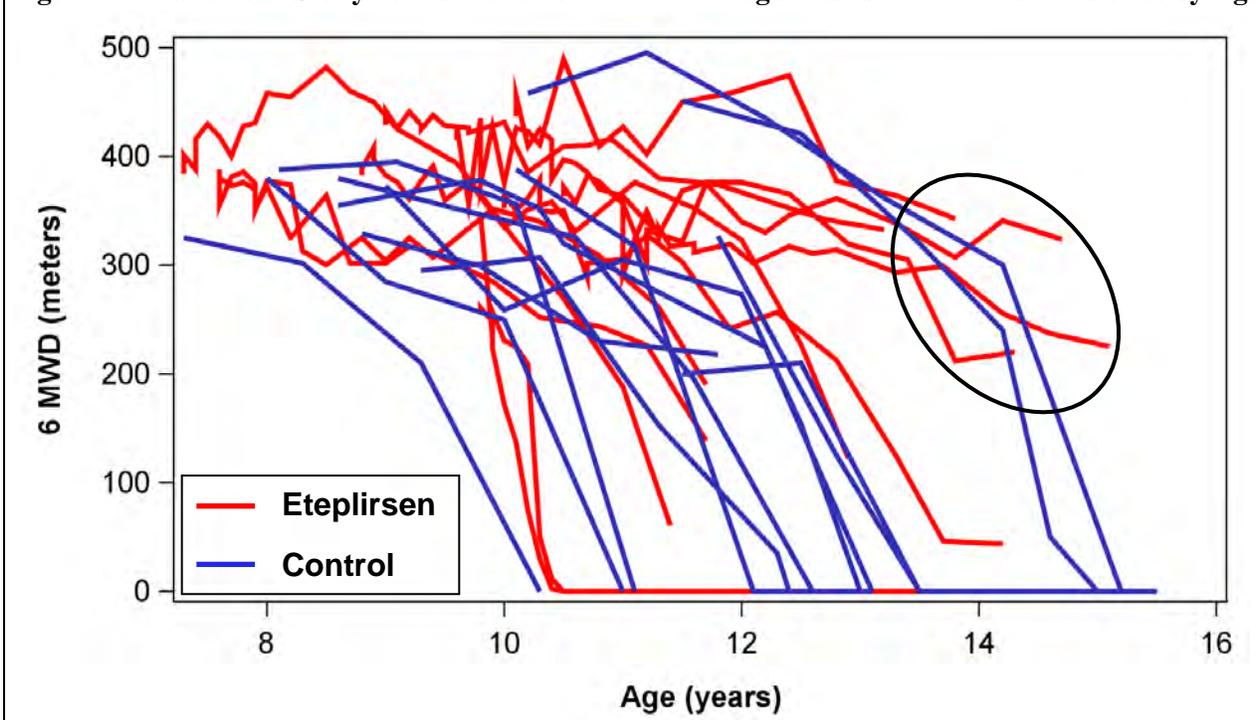
Study 202 was continued, therefore, with patients continuing to receive either 30 or 50 mg/kg/week eteplirsen. Numerous comparisons of physical function were planned between these 12 patients and the 13 patients in the external control group. Measures included 6-minute walk, rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA).

With two small groups of patients, there was no way to match patient pairs. Fortuitously, the mean ages and 6-minute walk distances were well matched at baseline, although the review team found that initial age of steroid use and baseline NSAA scores were dissimilar between groups – and both of these differences favored the eteplirsen group.

It is clear that some patients exited the registry to enroll in clinical trials. Thus, DMD patients who remained in the Italian and Belgian registries (the control group): 1) did not seek knowledge (or lacked knowledge) regarding applicable clinical trials into which they might have enrolled; 2) sought enrollment in trials but did not qualify; or 3) qualified for enrollment in a trial(s) but made a conscious decision not to participate. Obviously, such patients could differ substantially from patients in Study 201/202. The point is that there can be unknown factors beyond baseline age, weight, length of steroid use, and 6-minute walk distance that importantly affect outcomes.

The applicant presented the data by time-on-treatment, but because physical abilities change significantly with age in patients with DMD, the review team believes that the more meaningful way to display the longitudinal 6-minute walk data is by age (recognizing that both analyses have advantages and limitations, and that there is no ideal way to present these data). The 6-minute walk data are shown in Figure 12 as a function of age. The review team stresses that,

Figure 12: Patients in Study 202 vs. Patients in External Registries: 6-Minute Walk Distance by Age



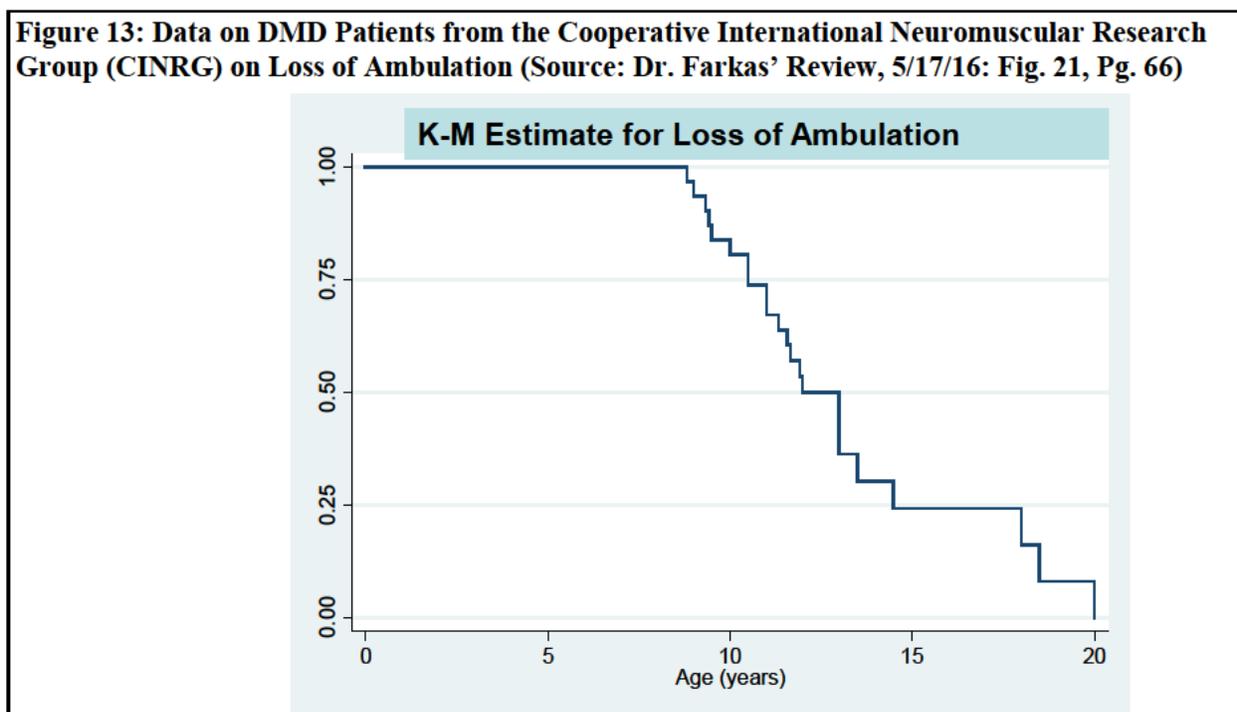
by simple visual inspection, the two groups show little difference in performance.

There are 4 patients in the eteplirsen group, ~14 to 15 years of age, who continue to retain good walking ability (inside the oval). There are 2 control patients in this age range who had been maintaining similar walking ability, but appear to have experienced a precipitous loss of ambulation between ages 14 and 15. As explained by the review team, there are concerns regarding the comparability of the assessments of these patients, and concerns about comparability of the groups in general.

The applicant's argument for accelerated approval is based on this comparison of 6-minute walk distance between the patients in Study 202 and the patients in the external control group from Italy and Belgium. The difference in 6-minute walk distance is certainly statistically significant. The problem is that the study was externally-controlled, and the statistical test was based on a non-randomized comparison.

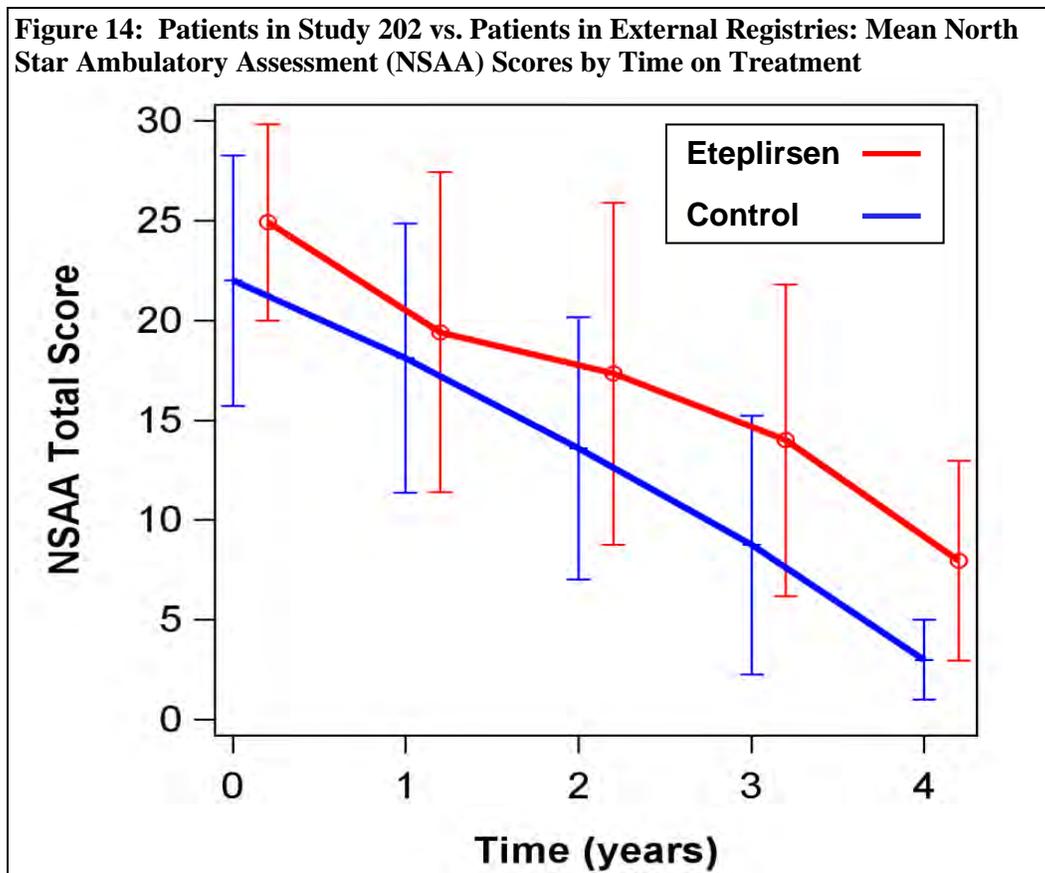
Data from the Cooperative International Neuromuscular Research Group (CINRG) provide an additional source of information on the natural history of patients with DMD. Figure 13 is a Kaplan-Meier (K-M) survival curve from CINRG showing time-to-loss of ambulation. Of note, 25% of patients remain ambulatory at age 17; their course seems quite consistent with that of patients from Study 201/202.

Figure 13: Data on DMD Patients from the Cooperative International Neuromuscular Research Group (CINRG) on Loss of Ambulation (Source: Dr. Farkas' Review, 5/17/16: Fig. 21, Pg. 66)



In summary, the review team strongly believes that patients on eteplirsen in Study 201/202 do not demonstrate a substantial treatment effect on walking velocity that clearly differentiates their course from the natural history of the disease. For a more complete description with comprehensive patient profiles, see the reviews of Drs. Breder and Farkas and the memo of Dr. Bastings.

Finally, as stressed by the review team, the data from other measures of physical function, i.e., rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA), show steady decline in the eteplirsen-treated patients that does not differ substantially from the decline in the external control group. The NSAA data are shown in Figure 14 by time on treatment (eteplirsen patients) or time since inception (registry patients). The NSAA is thought to be a comprehensive outcome measure, well reflecting the functional abilities of DMD patients. Of note, the downward trajectories of the two groups are indistinguishable (the lines are virtually parallel with equal slopes).



Patient Testimony/Advisory Committee:

In addition to the presentations made by the applicant and the review team at the April 25, 2016, Advisory Committee Meeting, there were testimonies from over 50 individuals and families, including most of the patients who were participating in Study 202. (Per email communication from (b) (4), one of the applicant’s consultants, 10 of the 12 patients testified and another patient had someone speak on his behalf.)

In addition, the applicant invited Christine McSherry, Executive Director of the Jett Foundation, to present “Patient and Caregiver Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne.”

The testimonies of these patients were quite consistent and remarkably positive: all were convinced that eteplirsen had made a substantial positive impact on their physical performance, improving numerous aspects of their lives.

It was noteworthy that a number of individuals who were in Study 201/202 reported *improvement* in physical function with eteplirsen treatment. For example, one patient stated that he had required a wheelchair at a school he had attended in the past, whereas he no longer needed a wheelchair at his present school. A video showed a boy who, prior to treatment, had some difficulty climbing up into the seat of a minivan. After receiving eteplirsen for several months, he was shown jumping up easily into the seat. In another video, a boy in the study threw a football, a tight spiral, with ease and finesse.

Many of the Committee members seemed obviously moved and deeply affected by these testimonies and videos, seemingly convinced that there was a treatment effect.

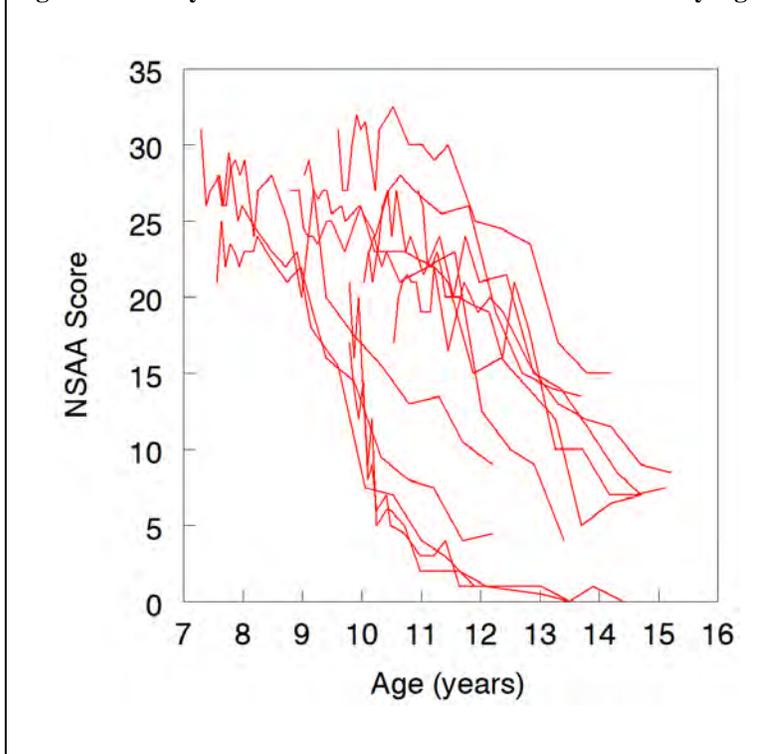
Importantly however, despite the claims of improvement made at the microphone at the Advisory Committee meeting, the review team did not find any patients in Study 201/202 with consistent improvement in physical performance as assessed by formal testing (6-minute walk, rise time, NSAA, 10-meter run). These tests have shown moderate to extreme declines in physical function for all patients (see NSAA data, Figure 15).

Thus, the review team and many on the Advisory Committee (including Benjamin Dupree, the patient representative with DMD), were unable to reconcile the patient testimonies with the data collected by the applicant: the testimonies spoke of *improvement*; the data showed *progressive worsening*.

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD.

The 7-member majority of the committee who voted "no" agreed that Study 201/202 was not a well-controlled study. Most cited problems with the controls. One member explained that a historically-controlled study *could* provide evidence of effectiveness, but that Study 202 did not. Two committee members noted that the original placebo-controlled portion of the study was

Figure 15: Study 201/202 – Individual NSAA Performance by Age



negative. One member who cited issues with the controls also noted that a single trial would be insufficient to provide substantial evidence.

The 3 members who voted that there was substantial evidence of effectiveness explained that the study results correlated with the testimonies presented by the public.

Commentary:

I agree with the Division, the Office of Biometrics, the Office of Clinical Pharmacology, and the Advisory Committee with respect to the lack of substantial evidence of effectiveness for eteplirsen. The review team elaborates on many factors that differ, or could differ, between the treatment groups – factors that could lead to a difference in outcomes. Externally-controlled trials are best-suited for diseases where progression is highly predictable and treatment effects are extreme. Although there appeared to be a difference in ambulation between patients in Study 202 and patients in the external control group, the effect size was not sufficient to be persuasive, given the inability to control bias in an externally-controlled study. As explained in ICH E10, "...the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." With only 12 patients in the trial and a moderate difference in walking velocity, the study falls short.

Finally, it is critical to note that no dose-limiting side effects were observed at either dose tested in Study 201/202, and even the most optimistic interpretation of the data is that patients experienced gradual decline in function – not stabilization. Even if one were to reach the conclusion that the applicant showed substantial evidence of dystrophin production, deserving of accelerated approval, investigation of higher doses would be imperative.

8. Safety

As explained in the clinical review, the number of subjects exposed was too small to provide an adequate assessment of safety. On the other hand, I also agree with the review team that the deficiencies in safety assessments would not likely be an issue for approvability in their own right had the drug been demonstrated to be effective. In other words, for a therapy that is shown to be effective in a serious condition where there are no approved drugs, we would approve a marketing application even with substantial risks, as long as we could write adequate instructions for use. Moreover, we would not delay approval of a marketing application because of uncertainty of risks. Instead, we would work with the applicant to obtain more extensive safety data post-approval. Such would be the case for this application if there were substantial evidence of effectiveness.

Of note, many patients in these studies are now receiving infusions through chronic indwelling catheters. Although we are not aware of any serious adverse events caused by infections, with approval of this drug there would undoubtedly be serious infections and possibly rare deaths eventually. The risk of an indwelling IV line in patients on chronic corticosteroids should be mentioned in labeling if the drug is approved.

Although neither immunogenicity nor allergic reactions have been reported with eteplirsen, immunogenicity testing would be advisable in ongoing trials. Moreover, given that these

patients may be naïve to Becker-type dystrophin, the potential for anti-dystrophin antibodies should be studied as well.

9. Advisory Committee Meeting

There were many important discussions at the April 25, 2016 Advisory Committee Meeting, and they are summarized above, in context.

10. Pediatrics

Duchenne Muscular Dystrophy is an orphan indication, not subject to the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

Site Inspections:

The site at Nationwide Children’s Hospital was inspected in 2014. See description and conclusions in Section 7, above, and, in particular, the summation and discussion in Dr. Breder’s review.

Dr. Ashutosh Rao conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) of the facilities at University of Iowa in Iowa City, IA and Sarepta Therapeutics Inc. in Corvallis, OR. The inspections confirmed that the blinding procedure, handling of the sample shipment, and the conduct of Western blot analyses of the samples from Study 301 (PROMOVI) were consistent as predefined in the protocol.

Name Review:

The Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, “EXONDYS 51,” is acceptable from both a promotional and safety perspective.

12. Labeling

I do not recommend approval, but if the drug were to be approved, the label would need to state that no clinical benefit has been established, and explain the effect on the surrogate endpoint in clearly understandable language (i.e., 0.3% or 3 parts in a thousand). Section 6 would need to note that safety is not well characterized.

13. Decision/Action

DMD is a rare genetic disease characterized by the near absence of functional dystrophin protein, leading inexorably to myocyte degeneration, muscle dysfunction and inflammation, severe disability, and death, robbing patients of their dignity along the way. Although steroids are thought to slow the course of the disease and are typically considered standard of care, they are by no means curative, and they have their own side effects.

The cause of DMD is well established – the absence of structural dystrophin protein in myocytes. There is wide belief in the medical/scientific community that restoration of functional dystrophin protein has a strong potential to ameliorate the disease.

Eteplirsen is a novel PMO that is designed to lead to translation of an abnormal but functional dystrophin protein – a protein that is produced in Becker muscular dystrophy, a far less severe form of muscular dystrophy. The data from RT-PCR show that the drug produces the intended Becker-type messenger RNA; we have no data on the extent of messenger RNA production.

As noted by the review team, the clinical data generated from study 201/202 do not provide evidence of efficacy. The aim of Study 201, the only randomized placebo-controlled study conducted by the applicant, was to assess dystrophin production in response to lower and higher eteplirsen regimens (30 or 50 mg/kg/week) vs. placebo. Results of the original analyses of Study 201, published in a major journal, were remarkably positive, and their publication led to widespread enthusiasm for the drug. Unfortunately, an FDA inspection found a number of important technical factors that rendered the data unreliable and uninterpretable: the Western blot analyses were sub-standard; there were also critical problems with the reading of the immunohistochemistry images. FDA recommended a blinded re-read of the images, but upon re-read of the images by 3 blinded pathologists using FDA-recommended procedures, there was no increase in dystrophin production.

Likewise, Study 201 did not meet its 1^o clinical endpoint, 6MWT, at Week 24. Two patients in the low-dose eteplirsen group became unable to ambulate early in the study, such that a proper intent-to-treat analysis of the 6-minute walk data nearly showed a statistically significant difference in favor of *placebo*.

The applicant switched all patients to active drug in Study 202, and has continued to follow the patients for 6-minute walk distance, NSAA, and rise time.

Study 202 did not meet its 1^o clinical endpoint, 6MWT, at 48 weeks.

The alternative analyses of Study 202 proposed by the applicant are based on comparison to an external control group obtained from registry patients in Italy and Belgium. Questions about comparability notwithstanding, analyses have not shown a clear separation of the disease course between eteplirsen-treated patients and external controls. Moreover, there is not a clear separation between eteplirsen-treated patients and patients in the CINRG registry. Thus, neither external control group suggests there is a treatment effect.

The Western blot analyses from Week 180 of Study 201/202 showed a low quantity (0.9%) of dystrophin; however, the study was not adequate and well controlled (the baseline level of dystrophin was not known with certainty), and the lack of correlation between results of Western blot and immunohistochemistry demonstrates a troubling lack of internal consistency.

Study 301, on the other hand, was an adequate and well-controlled study that provided substantial evidence of Becker-type dystrophin production in response to eteplirsen. The mean change in Becker-type dystrophin with treatment was 0.22% to 0.32%, depending on the method used to impute values less than the lower limit of quantification. Although all members of the review team believe that Becker-type dystrophin is an appropriate surrogate endpoint, the mean quantity of dystrophin produced in Study 301 was minute by any standard. In considering

responders, even the largest responder in Study 301 produced only 1.33% of normal dystrophin, which is thought by many authorities to be insufficient. No other patient produced 1% dystrophin in response to treatment.

Recognizing that the threshold for the effect size needed to be 'reasonably likely' to predict clinical benefit is not known, the view provided in the literature suggests that at least 3% of normal dystrophin is inadequate, and levels perhaps much more, a minimum of 10%, would be necessary for detectable clinical benefit. The finding in Study 301, an increase in the range of 0.22 to 0.32% of normal, is an order of magnitude below this level.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will be capable of ameliorating the fundamental genetic defect of DMD, but the effect size seems insufficient at the tested doses.

Various individuals have opined that there appears to be some evidence that some patients are producing dystrophin in response to eteplirsen; however, such optimism fails to reach the legal threshold of 'reasonably likely to predict clinical benefit' required for accelerated approval.

Accelerated approval of this NDA based primarily on the change in Becker-type dystrophin in Study 301 would be problematic for these reasons:

1. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.22% is considered adequate to support accelerated approval, then the question arises as to whether there is any statistically significant change that would be too small to support accelerated approval. Similarly, if a response had been defined as a treatment effect of 1%, there would have been only one (out of 12) responders in Study 301.

If we were to adopt the concept that, for rare diseases, accelerated approval can be supported by any statistically significant change in an appropriate surrogate (or by a response in a single patient), we would enable accelerated approval of numerous drugs for rare diseases. No doubt there are some who would applaud this as a regulatory advance, but these are typically the kinds of findings that support Breakthrough Designation, not approval. If accelerated approval based on any change in a surrogate endpoint is what is meant by regulatory flexibility and this is the new normal, a new approval pathway is clearly needed.

With lowering of the standard for accelerated approval, the result would be a world where traditional clinical trials are abandoned in favor of small proof-of-concept studies designed to show any level of production of a target protein – e.g., a statistically significant effect in a paired pre- vs. post-treatment analysis that is clinically meaningless. There would be no reason to pursue placebo-controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a substantial disincentive to the conduct of such trials. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.

2. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, the dose is sub-therapeutic. Moreover, the short 3.5-hour half-life of eteplirsen by no means supports a weekly dosing regimen. I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic.

Imagine that 100 years ago a promising drug called penicillin is discovered – a potential cure for pneumococcal pneumonia – but the drug is difficult to produce and expensive. A dose of 5 mg weekly has been shown to have statistically significant bactericidal effects on *Streptococcus pneumoniae*. Would it be ethical to give the drug accelerated approval based on this finding and allow marketing of a dose of 5 mg, absent additional information? (The therapeutic dose is ~2 logs higher than 5 mg.) Patients who might receive a lifesaving therapy (i.e., a higher dose) would die because the dose is too low.

Despite considerable pressure from the DMD patient community and many well-intentioned members of the public who have lobbied on their behalf, I am unable to reach the conclusion that the applicant has provided substantial evidence to support either conventional or accelerated approval of eteplirsen for the treatment of DMD. This view is in agreement with the unanimous opinions of members of the review team from the Division of Neurology Products, the clinical pharmacology review team, and the biostatistics review team. The Advisory Committee was under intense and near-incessant pressure from a large public audience, urging them to believe that eteplirsen was effective, and life changing in some circumstances. Emotions in the room ran high. In spite of this pressure, that majority of the Advisory Committee voted against both conventional and accelerated approval.

In a June 3, 2016 letter from Dr. Janet Woodcock, the applicant was advised that “If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval....” It is difficult to consider production of 2 to 3 parts per thousand as a “meaningful” change. To put this effect into perspective, if a normal amount of dystrophin were equivalent to a \$5 bill, this change would be equivalent to a penny.

With all of this information at hand, most sponsors would have concluded that exploration of higher doses was needed; however, this applicant chose instead to trumpet the preliminary findings from their 12-patient phase 1/2 study, convincing many in the DMD community that the drug was highly effective, and unleashing a public media campaign (with support of many politicians) to approve the drug. The reality is that FDA is a science-based organization. We do not – and should not – make approval decisions based on patient anecdotes or campaigns through social media.

I strongly agree with the decisions of Dr. Bastings, reviewer staff in the Division, the Office of Biometrics, and the Office of Clinical Pharmacology to issue a complete response for this NDA. I also agree that it would be desirable to provide access to this drug for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

Path Forward:

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at a dose of 30 and 50 mg/kg/week are adequate, but they do not support efficacy.

We remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the 1° endpoint, again, testing higher doses.

The applicant is continuing to enroll the PROMOVI study, an open-label, multi-center, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

The 1° endpoint is change in 6-minute walk test distance from baseline. A 2° endpoint is the percentage of dystrophin-positive fibers, as assessed by immunohistochemistry. Patients undergo muscle biopsies at baseline and various time points to assess dystrophin production.

My suggestion for a path to approval is to randomize patients in the ongoing PROMOVI study to:

- 1) remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blind to treatment group. For accelerated approval, the 1° endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the 1° endpoint would be a test(s) of physical performance such as rise time or the NSAA.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, want to know if higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients assigned to placebo, this concern would not exist in this study. And if the applicant were to forego immunohistochemistry studies, needle biopsies with local anesthesia (rather than open biopsies under more intensive anesthesia) would be sufficient.

This study design would simultaneously address another concern that I believe has been underappreciated by many. As noted above, it would be problematic in my view to approve a dose of 30 mg/kg/week, presumably leading to a dystrophin increase of ~0.3%, when it is

known that this dose fails to prevent the decline in physical function and yet produces no overt toxicity. The monkey data (Table 1) suggest that much higher doses might have a far greater effect on exon skipping, an impact that might prevent disease progression. Thus, it seems imperative to study higher exposures.

14. Final

Many of us would wish to approve this drug if we could. DMD is a horrible disease and there are no approved treatments. FDA takes seriously the patient perspective and our congressional mandate to be flexible. But patient-focused drug development is about listening to patient perspectives about what matters to them; it is not about basing drug approvals on anecdotal testimony that is not corroborated by data.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)

- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 35\%$ and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: 09/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

- a. Calculate the total dose of EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.
- b. Allow vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.
- c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.
- d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.
- e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.
- f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6

patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week [see *Clinical Studies (14)*].

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended [see *Dosage and Administration (2.1)*].

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week¹ EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8)	Placebo (N=4)
	%	%
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

¹ 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥ 30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in $\geq 10\%$ of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated 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, including pediatric patients [see *Clinical Studies (14)*].

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

There is no experience with overdose of EXONDYS 51.

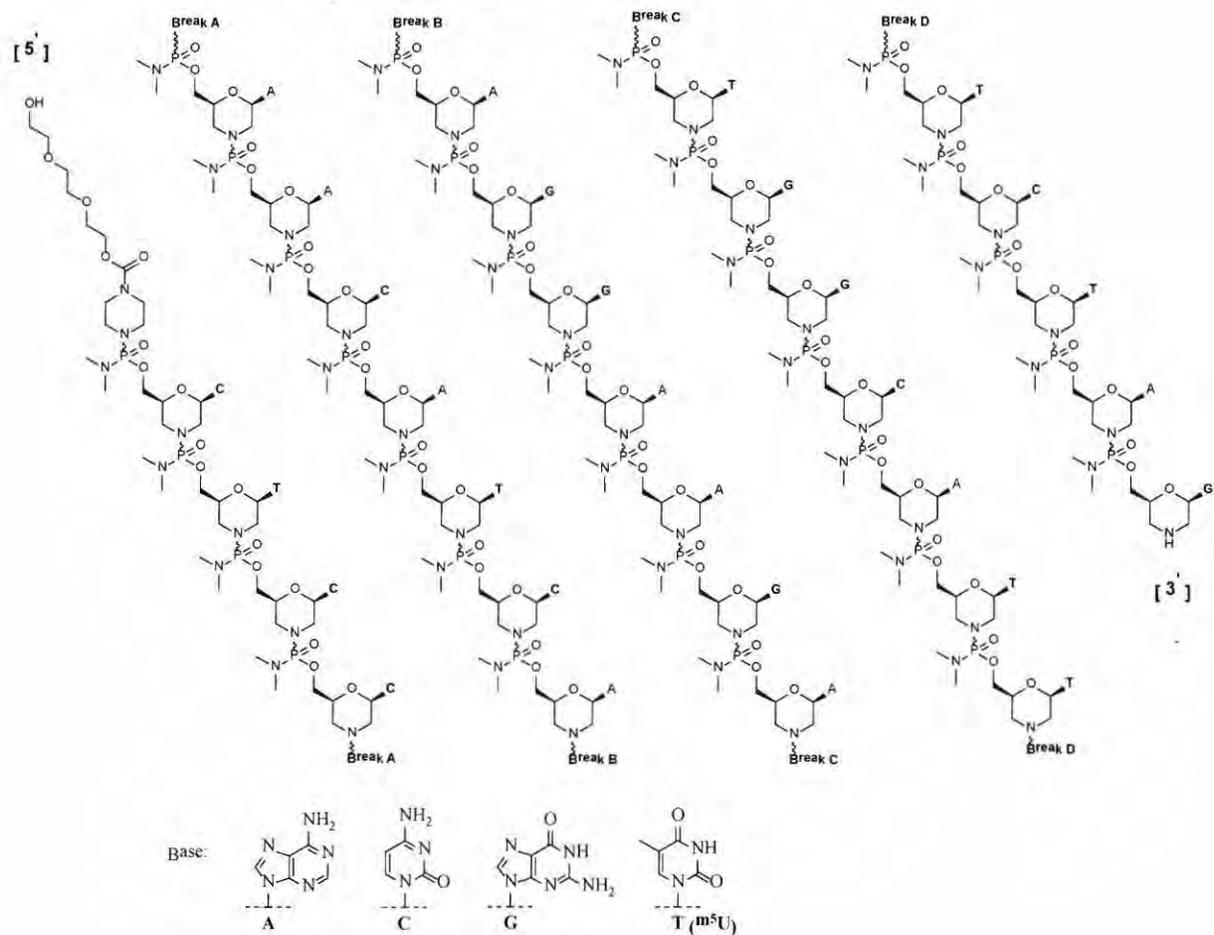
11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 0.2 mg potassium chloride, 0.2 mg potassium phosphate monobasic, 8 mg sodium chloride, and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [see *Clinical studies* (14)].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 [see *Clinical studies (14)*]. The median increase in truncated dystrophin in Study 3 was 0.1% [see *Clinical Studies (14)*].

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (V_{ss}) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max} . Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC)

in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was $0.16\% \pm 0.12\%$ (mean \pm standard deviation) of the dystrophin level in a healthy subject and $0.44\% \pm 0.43\%$ after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
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1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; $p=0.008$

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA



NDA 206488

GENERAL ADVICE

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

This letter is in response to your email of June 2, 2016, to Janet Woodcock, M.D., in which you agreed to perform Western blots on baseline and Week 48 biopsies from eteplirsen-treated patients to assess dystrophin content. We will work with you on the protocol and analysis plan, and on the dates for FDA observers to be present during the procedures.

We agree to have an FDA observer present at the Iowa site to monitor tissue sampling and blinding procedures, and to have an observer present at the Corvallis site during performance of the Western blot procedure. We also understand that Corvallis is not a GLP facility.

We understand that a new normal control will need to be established to generate the standard curve of a serially-diluted normal comparator as part of these procedures. Please confirm the healthy dystrophin genotype and phenotype of this new control and compare side-by-side with the limited previous healthy control you have available. Confirm that the validation parameters and acceptance criteria for the new healthy control are comparable to those for the previous healthy control used with the Week 180 samples (e.g., linearity of the serially diluted sample, %RSD).

You should provide each of the relevant protocols for our review that describe the methods you propose to use for testing dystrophin, including those related to tissue acquisition at the clinical site(s), processing, blinding, and shipping procedures at the University of Iowa or elsewhere, tissue quality control before analysis, validation of the new normal control, and Western blotting at the Corvallis location.

You should implement appropriate quality control measures including strict blinding procedures to ensure that the integrity of the other primary and secondary assessments is not compromised as a result of this specific dystrophin investigation.

If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to

grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).

To allow for prompt approval, should your dystrophin analysis prove successful, we will work with you over the next several weeks on completing labeling negotiations to the degree possible and on necessary postmarketing requirements and commitments.

We request that you not publicly communicate the specific details of this plan until after completion in order to allow maximum procedural efficiency.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
06/03/2016

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s):	NDA 206488
Communication Type:	Correspondence
Communication Group:	NDA Action
Communication Name:	Accelerated Approval
Communication ID:	COR-NDAACTION-04
Drafted by:	Choy, Kelley, Ware 9/16/16
Clearance History:	M Chelliah / Heimann (CMC) 6/24/16, 6/30/16; Yasuda/Hughes 6/28/16, Yasuda 7/20/16, 8/8/16, 9/16/16; SRT 6/30/16, 7/18/16, 7/19/16; Locicero 7/1/16; Bastings 7/1/16, 9/16/16; J Woodcock
Finalized:	
Filename:	
Signatory Authority:	NMEs and 351(a) BLAs must be signed by the Office Director or Deputy Office Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use when approving an NDA under 21 CFR 314.510 (approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity).
Notes:	

Version: 02/11/2016

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA 206488

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We acknowledge receipt of your major amendment dated January 8, 2016, which extended the goal date by three months.

This new drug application provides for the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206488.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, we refer to your June 10, 2016, submission in which you commit to implement the carton container label revisions requested in our June 6, 2016, correspondence. Specifically, you agree to remove the reference to the compendial grades from the carton labels at the time of next printing, but no later than 120 days post-approval, and to notify us of this change via submission of a "Changes Being Effected" supplemental application.

PRODUCT QUALITY

Based on evaluation of the stability data provided, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°C).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number: PRV NDA 206488. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of

times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2016. This requirement, along with required completion dates as agreed upon on September 16, 2016, is listed below.

- 3095-1 In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Draft Protocol Submission:	10/2016
Final Protocol Submission:	04/2017
Trial Completion:	11/2020
Final Report Submission:	05/2021

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocol to your IND 077429 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s).**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity or an unexpected serious risk of immunogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3095-2 A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2016
Final Protocol Submission:	03/2017
Study Completion:	04/2020
Final Report Submission:	06/2020

- 3095-3 A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2016
Final Protocol Submission: 01/2017
Study Completion: 05/2018
Final Report Submission: 06/2018

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies.

- 3095-4 A study to evaluate:
1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
 2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2017
Final Protocol Submission: 08/2017
Study Completion: 12/2017
Final Report Submission: 02/2018

Additional guidance for immunogenicity assay development, though more specific for therapeutic protein products, may be found in the draft guidance: "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products"

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocols prior to initiation of the studies.

Submit the protocols to your IND 077429, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-5 Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2016
Final Protocol Submission: 04/2017
Trial Completion: 04/2021
Final Report Submission: 10/2021

A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3095-6 Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

- 3095-7 Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) results that were observed at lot release.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

Submit clinical protocols to your IND 077429 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic

License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)

- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: 09/2016

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 [see *Clinical Studies (14)*]. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

- a. Calculate the total dose of EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.
- b. Allow vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.
- c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.
- d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.
- e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.
- f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6

patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week [see *Clinical Studies (14)*].

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended [see *Dosage and Administration (2.1)*].

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week¹ EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8)	Placebo (N=4)
	%	%
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

¹ 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥ 30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in $\geq 10\%$ of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated 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, including pediatric patients [see *Clinical Studies (14)*].

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

There is no experience with overdose of EXONDYS 51.

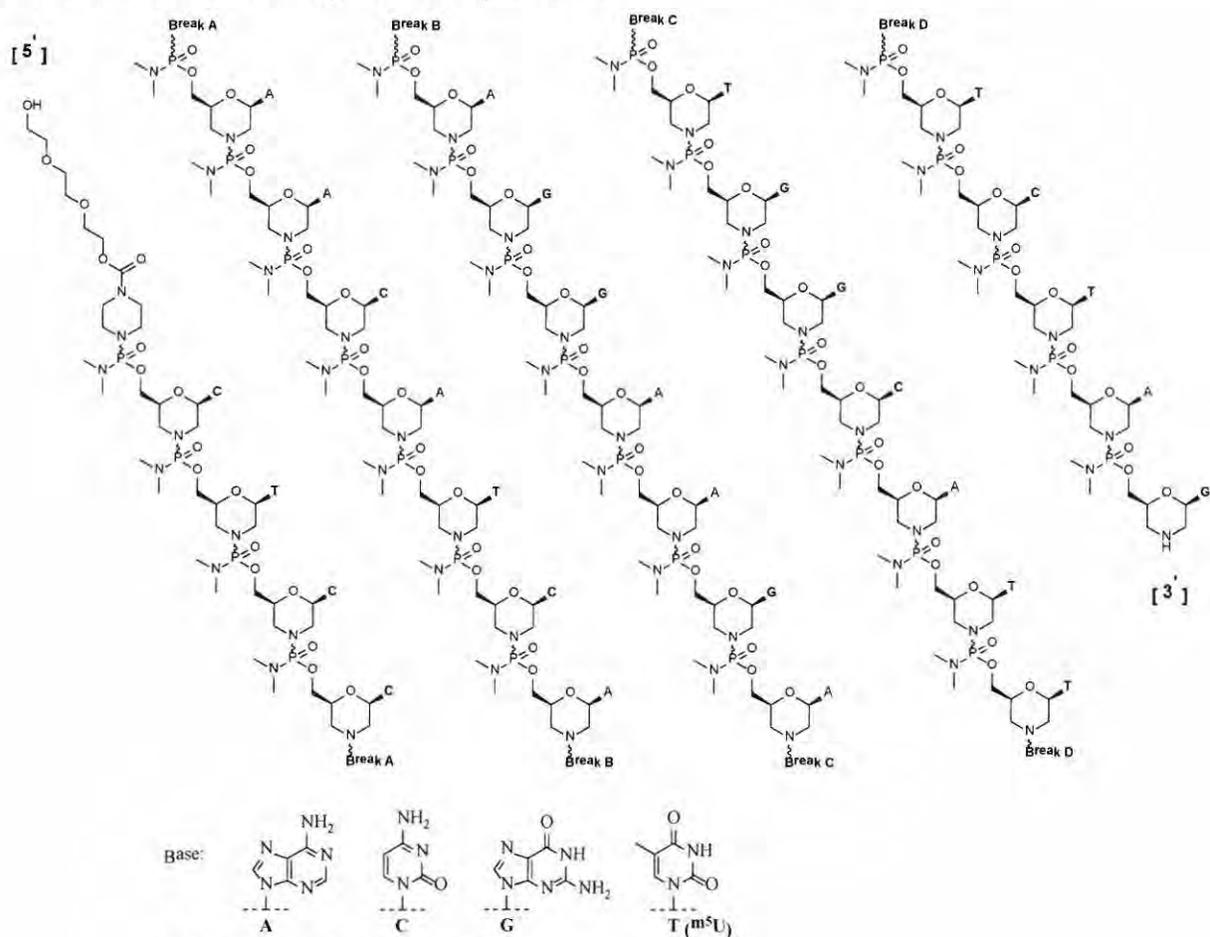
11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 0.2 mg potassium chloride, 0.2 mg potassium phosphate monobasic, 8 mg sodium chloride, and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [see *Clinical studies* (14)].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 [see *Clinical studies (14)*]. The median increase in truncated dystrophin in Study 3 was 0.1% [see *Clinical Studies (14)*].

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (V_{ss}) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max} . Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC)

in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was $0.16\% \pm 0.12\%$ (mean \pm standard deviation) of the dystrophin level in a healthy subject and $0.44\% \pm 0.43\%$ after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
----------------	---------------------------------	--------------------------------	---

1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; $p=0.008$

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

From: [Unger, Ellis](#)
To: [Pennington, Caitlin](#)
Cc: [Ligon, Sharnell \(CDER\)](#); [Vail, Victor H](#); [Dunn, Billy](#); [Woodcock, Janet](#); [Jenkins, John K](#); [Temple, Robert](#); [Bastings, Eric](#); [Kraus, Tom](#)
Subject: RE: meeting with review team
Date: Monday, September 12, 2016 2:12:00 PM

OK, sounds good. The invitees from DNP should include:

Billy Dunn
Eric Bastings
Jacqueline Ware
Lois Freed
Nicholas Kozauer
Chris Breder
David Hawver
Yuet (Fannie) Choy
Tracy Peters

Thanks,

Ellis

From: Pennington, Caitlin
Sent: Monday, September 12, 2016 12:53 PM
To: Unger, Ellis
Cc: Ligon, Sharnell (CDER); Vail, Victor H; Dunn, Billy; Woodcock, Janet; Jenkins, John K; Temple, Robert; Bastings, Eric; Kraus, Tom
Subject: RE: meeting with review team

Hi Ellis,

Dr. Califf feels that it is imperative to meet with the Division tomorrow.

Thanks!

Caitlin

From: Unger, Ellis
Sent: Monday, September 12, 2016 10:50 AM
To: Pennington, Caitlin
Cc: Ligon, Sharnell (CDER); Vail, Victor H; Dunn, Billy; Woodcock, Janet; Jenkins, John K; Temple, Robert; Bastings, Eric
Subject: RE: meeting with review team

Caitlin,

I spoke with Billy Dunn (the Division Director) and Eric Bastings (the Deputy Division Director). If the Commissioner feels that it is imperative to meet with the Division before the action is taken, then Eric and I are available to meet at 5 PM tomorrow, but Billy would have to participate by phone (he is away attending a neurology meeting tomorrow).

But we all think it would be more productive to have a meeting with the whole review team (with Billy Dunn in attendance), and also better to wait until the team has had the opportunity to digest the Commissioner's memo.

Bottom line – if the Commissioner wants to talk with the principals prior to the action, we can do that tomorrow at 5, although Billy Dunn will have to participate by phone. Otherwise, it would be better to have a more inclusive meeting once people have read the Commissioner's memo – even if the meeting takes place after the action.

Ellis

From: Pennington, Caitlin
Sent: Monday, September 12, 2016 8:05 AM
To: Vail, Victor H; Ligon, Sharnell (CDER); Unger, Ellis; Dunn, Billy
Subject: FW: meeting with review team

Good Morning All,

Are you or your principals available tomorrow at 5 pm?

Thanks!

Caitlin

From: Jenkins, John K
Sent: Sunday, September 11, 2016 9:36 PM
To: Kraus, Tom
Cc: Califf, Robert; Pennington, Caitlin; Woodcock, Janet; Unger, Ellis; Dunn, Billy; Vail, Victor H
Subject: Re: meeting with review team

Victor Vail manages my calendar. Ellis Unger and Billy Dunn can help with collecting the review team. I will be as flexible as possible knowing that Rob's calendar is a challenge this week. I hope the meeting can be in person.

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Kraus, Tom
Sent: Sunday, September 11, 2016 9:27 PM
To: Jenkins, John K
Cc: Califf, Robert; Pennington, Caitlin; Woodcock, Janet
Subject: meeting with review team

John,

I understand you and Dr. Califf have discussed finding an opportunity for him to meet with the review team regarding eteplirsen.

Caitlin Pennington (copied) will be able to help us find a time that works for Dr. Califf. Who can she connect with to find a time that works for you and the team and to help us identify who should be included? We're hoping to set up the meeting before Dr. Califf needs to leave for a flight Tuesday evening.

Tom

From: [Pennington, Caitlin](#)
To: [Unger, Ellis](#)
Cc: [Ligon, Sharnell \(CDER\)](#); [Vail, Victor H](#); [Dunn, Billy](#); [Woodcock, Janet](#); [Jenkins, John K](#); [Temple, Robert](#); [Bastings, Eric](#); [Kraus, Tom](#)
Subject: RE: meeting with review team
Date: Monday, September 12, 2016 12:52:48 PM

Hi Ellis,

Dr. Califf feels that it is imperative to meet with the Division tomorrow.

Thanks!

Caitlin

From: Unger, Ellis
Sent: Monday, September 12, 2016 10:50 AM
To: Pennington, Caitlin
Cc: Ligon, Sharnell (CDER); Vail, Victor H; Dunn, Billy; Woodcock, Janet; Jenkins, John K; Temple, Robert; Bastings, Eric
Subject: RE: meeting with review team

Caitlin,

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To: Kraus, Tom
Cc: Califf, Robert; Pennington, Caitlin; Woodcock, Janet; Unger, Ellis; Dunn, Billy; Vail, Victor H
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Cc: Califf, Robert; Pennington, Caitlin; Woodcock, Janet
Subject: meeting with review team

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Caitlin Pennington (copied) will be able to help us find a time that works for Dr. Califf. Who can she connect with to find a time that works for you and the team and to help us identify who should be included? We're hoping to set up the meeting before Dr. Califf needs to leave for a flight Tuesday evening.

Tom

From: Unger, Ellis
To: Woodcock, Janet
Cc: Peters, Tracy; Dunn, Billy; Freed, Lois M; Bastings, Eric; Choy, Fannie (Yuet); Jenkins, John K
Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen
Date: Monday, September 12, 2016 11:12:57 AM
Attachments: FDAedits-COMPLETE_Round6_28July16-Eteplirsen PI to Sarepta.docx

Janet,

Here is the latest version of the label. In section 12.2, the company had stated: [REDACTED] (B) (4)
[REDACTED]”

The corollary, of course, is that approximately half of patients showed nothing. Thus, to the extent that the results of 301 can be extrapolated to the to-be-marketed population, approximately half of patients will get nothing in exchange for the risks, inconveniences, costs, and false hope of a life-long indwelling IV line and weekly eteplirsen infusions.

What is clear is that the Western blot data from study 301 are not normally distributed; therefore, representing those data as their mean is somewhat deceptive. Typically, we express such data by their median, which is 0.1% in this case.

We put the median increase in sections 12.2 and 14 of the label, and the company objected.

I don't believe we ever responded to Shamim Ruff, but our view is that the median should be reported in both sections (although we all also allowed showing the mean).

Once we get the company's acquiescence on this, the label is done.

Ellis

From: Choy, Fannie (Yuet)
Sent: Friday, July 29, 2016 6:55 PM
To: Bastings, Eric; Unger, Ellis
Cc: Peters, Tracy; Dunn, Billy; Choy, Fannie (Yuet); Farkas, Ronald; Freed, Lois M
Subject: FW: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Hi,

Sarepta does not like the proposed text "...median increase in truncated dystrophin in Study 3 was 0.1%." Please see email below.

Thanks

Fannie

From: Shamim Ruff [mailto:SRuff@Sarepta.com]
Sent: Friday, July 29, 2016 3:34 PM
To: Choy, Fannie (Yuet)
Cc: Shamim Ruff

Subject: RE: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Fannie

We were somewhat surprised to receive this latest set of comments from the Division given that we already had quite a number of requests on the label, all of which were accepted by us. We have reviewed the latest set of comments and accept all of them except the following two:

- Section 12.2: We believe it is redundant to include the median value for dystrophin as Table 2 in section 14 includes the dystrophin values from all 12 patients.
- Section 14: As above, we also believe it is redundant to include the median value for dystrophin as Table 2 includes the dystrophin values from all 12 patients.

Please note that we are happy to have a telephone call early next week (Monday or Tuesday) if we need to discuss otherwise please confirm that this is now the final version of the USPI.

Regards,
Shamim

Shamim Ruff

SVP Regulatory Affairs and Quality
p 617-274-4009 c [REDACTED] (b) (6)
e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Thursday, July 28, 2016 5:27 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Proposed Labeling Text: NDA 206488 / eteplirsen

Dear Shamim,

Attached please find the FDA proposed labeling text for package insert (PI) for your pending application: NDA 206488 / eteplirsen submitted on June 26, 2015. The base document is the firm's version dated July 12, 2016 with FDA proposed changes identified via track changes.

We have incorporated the proposed edits after additional review of the PI. Please review and provide any edits as tracked changes using our proposed text as the base.

FDACDER0001055

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE 1/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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11 pages of draft labeling have been withheld as b(4) immediately following this page

From: [Califf, Robert](#)
To: [Woodcock, Janet](#); [Sherman, Rachel](#)
Subject: RE: Your question about confirmatory evidence
Date: Monday, September 12, 2016 10:06:57 PM

Interesting if there wasn't so much emotion.
rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Monday, September 12, 2016 7:09 PM
To: Califf, Robert; Sherman, Rachel
Subject: Your question about confirmatory evidence

Rob to answer your question about the confirmatory [REDACTED] (b) (4)

[REDACTED]. I looked up the reg after we talked about this, and I talked to Rachel about it. My idea has always been to confirm the surrogate in a population where the community has not lost equipoise. Frequently this is done in oncology, they study a different disease phase or something other than what they approved it for in the confirmatory study.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The reg says "the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation(sic) of the surrogate endpoint to clinical benefit..." I read this to say that the sponsor must do a confirmatory trial, but if the uncertainty about the validity of the surrogate to the clinical benefit can be answered in another way, that will do as well. I'd be interested in what Rachel thinks.

The only issue here is a molecular medicine one— [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]

I don't think we should put this in the responsive Q&As because they are for the press officers to answer questions and this is too complicated. But that is what I have advocated for even before the application was filed, and urged the Division to move [REDACTED] (b) (4) along. Much of the community had no appetite for a placebo controlled trial in [REDACTED] (b) (4)—I think it would have been very difficult to accomplish. jw

From: [Unger, Ellis](#)
To: [Woodcock, Janet](#)
Subject: Re: sarepta
Date: Monday, September 12, 2016 8:19:51 AM

Yes. Billy told them last night.

Sent from my BlackBerry.

From: Woodcock, Janet
Sent: Monday, September 12, 2016 8:10 AM
To: Unger, Ellis
Subject: sarepta

Is the division aware of the decision yet? Rob is asking me about what needs to be done yet, per John J's email. My impression is that only a final exchange on the label. JW

From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: RE: Approval timing
Date: Sunday, September 11, 2016 1:30:56 PM

Are you around this evening to check in on this?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Sunday, September 11, 2016 12:58 PM
To: Califf, Robert
Subject: Approval timing

Rob it will take several weeks for redaction of the entire package. So if we want to release everything at the time of approval they should start soon. I will be out of town on a long planned short vacation Monday a week but Doug or Rich can be the spokesperson. JW

From: [Califf, Robert](#)
To: [Jenkins, John K](#); [Woodcock, Janet](#); [Unger, Ellis](#)
Subject: RE: Follow up on Eteplirsen
Date: Sunday, September 11, 2016 7:12:50 AM

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

3. Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have

to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

4. Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
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Cc: Jenkins, John K
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John

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: FW: Approval letter for DMD and labeling
Date: Thursday, September 08, 2016 5:07:05 PM
Importance: High

FYI. Dr. Califf is fine with Dr. Unger sharing his decision with the division. Should be receiving the letter soon. sl

From: Ligon, Sharnell (CDER)
Sent: Thursday, September 08, 2016 4:54 PM
To: Unger, Ellis
Subject: RE: Approval letter for DMD and labeling
Importance: High

Dear Dr. Unger,

Thank you for your patience. Dr. Califf is fine with you sharing the decision to the division **only**. The labeling piece is no longer needed, therefore, we just need a copy of the approval letter.

Kind Regards,

Sharnell

From: Unger, Ellis
Sent: Thursday, September 08, 2016 10:03 AM
To: Ligon, Sharnell (CDER)
Subject: Re: Approval letter for DMD and labeling

I'll have to check and see if I have them. The Division has "version control" for these documents, and the Division is still not aware of the plan for action.

Can you find out if it would be OK to apprise the Division re: approval?

Sent from my BlackBerry.

From: Ligon, Sharnell (CDER)
Sent: Thursday, September 8, 2016 9:47 AM
To: Unger, Ellis
Subject: Approval letter for DMD and labeling

Good Morning Dr. Unger,

Dr. Califf has asked Dr. Woodcock if she can send over the draft approval letter and labeling for DMD. However, Dr. Woodcock is out of the office so I was asked to reach out to you directly to retrieve this information. Can you kindly assist me?

Thanks

Sharnell

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: FW: Approval letter for DMD and labeling
Date: Thursday, September 08, 2016 11:54:56 AM

FYI. Please see Ellis response below that I shared with Rachel and Dr. Califf. We are awaiting Dr. Califf's response as well as Liz to see if we should let the division know.

Sharnell

From: Unger, Ellis
Sent: Thursday, September 08, 2016 10:03 AM
To: Ligon, Sharnell (CDER)
Subject: Re: Approval letter for DMD and labeling

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Thanks

Sharnell

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: FW: approval letter
Date: Thursday, September 08, 2016 9:25:15 AM

Please let me know if you want me to assist with the below.

Sharnell.

From: Califf, Robert
Sent: Thursday, September 08, 2016 9:21 AM
To: Woodcock, Janet
Cc: Sherman, Rachel
Subject: approval letter

Janet,

Can I see the approval letter to make sure my memo is consistent with what is there?

Thx

Rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: talked with both Ellis and John
Date: Wednesday, September 07, 2016 9:45:14 PM

No surprises.

rmc

From: [Califf, Robert](#)
To: [Woodcock, Janet](#); [Unger, Ellis](#)
Cc: [Borio, Luciana](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: highly confidential
Date: Tuesday, August 30, 2016 1:46:22 PM
Attachments: [Recommendation References.zip](#)
[SDR Recommendation Regarding Eteplirsen Final.pdf](#)

Janet and Ellis,

Enclosed is a copy of the Board's recommendation and Lu's reflection in the form of an addendum. Please keep this in strict confidence, but I would like to hear from you by close of business Thursday if you have any major concerns or points of clarification. I have reviewed my reasoning with both of you, pending my conclusion which I will finalize over the weekend.

I do not want to launch a round of "lobbying" and know that you will keep this close and professional.

I appreciate your diligence and attention to procedure.

Regards

rmc

recommendation must reflect the SDR Board's underlying rationale, along with minority views among the members, for those findings.⁶

In conducting its evaluation, the SDR Board reviewed pertinent aspects of the Center's administrative file for the eteplirsen NDA and interviewed Dr. Unger, Dr. Woodcock, one member of the review team for the NDA, who requested anonymity, and Virginia Behr, the Ombudsman for CDER. Based on its review, the SDR Board has determined that the processes followed by CDER provided Dr. Unger with an adequate opportunity to present his scientific views and that CDER considered all relevant evidence. As Chair of the SDR Board, I therefore recommend that you do not remand this matter to the Center Director for further action.⁷ However, there are additional considerations meriting your attention, which I describe below. Furthermore, the SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit.

BACKGROUND

1. *Eteplirsen and DMD*

Dr. Unger provides an overview of eteplirsen and DMD in his appeal.⁸ In short, DMD is a genetic disorder with catastrophic effects on its sufferers:

[DMD] is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene[,] . . . [which] disrupt the messenger ribonucleic acid (mRNA) reading frame [and] lead[] to the absence or near-absence of dystrophin protein in muscle cells. . . . Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. . . . [and a concomitant] loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.⁹

There are no FDA-approved therapies for DMD.¹⁰ Sarepta has designed eteplirsen to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded from the resulting mRNA:¹¹

[B]y restoring [] the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug

⁶ *Id.* at 13.

⁷ *See id.* ("The Commissioner will review the [SDR Board's] recommendation and render a final decision on . . . whether the dispute should be remanded to the Center Director for corrective action" and "work with the Center Director to determine what corrective actions must be taken, if any.")

⁸ Unless otherwise indicated, Drs. Unger and Woodcock appear to agree as to the background provided in this section.

⁹ Appeal at 2.

¹⁰ *Id.*

¹¹ The charity, Muscular Dystrophy UK, has a nice description of the technology underpinning eteplirsen, which can be accessed at: <http://www.muscular dystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/>.

would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.¹²

In attempting to establish that eteplirsen is safe and effective for the treatment of DMD, and thus meets one of the standards for approval in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Sarepta has submitted data from three clinical studies:

Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study.¹³

Dr. Unger further explains:

The endpoints for [the three] studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.¹⁴

Immunohistochemistry (IHC) analysis looks at thin slices of muscle biopsies to see if dystrophin is present or absent. Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. Western blot analysis assesses how much dystrophin is present.

For Study 201/202, Sarepta submitted Western blot and IHC analysis evaluating proteins in muscle samples obtained from the twelve patients before the study and then again at twelve, 24, and 48 weeks.¹⁵ “The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.”¹⁶ Because CDER also determined that the conditions under which the original IHC analysis was performed were inadequate, including that the reader was not masked to sequence and time, the Center requested a re-reading of the stored images by three masked pathologists under different conditions.¹⁷ The IHC results from the reread were not nearly as favorable, as compared to the initial IHC results reported by Sarepta.

¹² Appeal at 2.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.* at 4, 8.

¹⁶ *Id.* at 4.

¹⁷ Unger Decisional Memorandum at 12-13.

The re-read showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group[] (. . . [T]he type-I error rate was not controlled for multiplicity.)¹⁸ Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.¹⁹

For Study 201/202, CDER also worked with Sarepta to improve the Western blot assays, and researchers performed repeat biopsies on eleven of twelve patients at Week 180.²⁰ Only three of the eleven patients had stored baseline samples that were adequate for evaluation, and so baseline samples were obtained from six additional patients external to Study 201/202.²¹ Dr. Unger also notes that all baseline samples were obtained from a different muscle group than the samples obtained at Week 180.²² Based on its own analysis of the IHC data, Sarepta claimed a remarkable increase of dystrophin immunostaining at Week 180: from 1.1% ± 1.3% positive muscle fibers at baseline to 17.4% ± 10.0% positive fibers at Week 180.²³ The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers.²⁴ Dr. Unger remarked that the lack of concordance between the IHC and the Western Blot results is “striking” and also noted that FDA did not verify the integrity of the IHC results.²⁵ As previously noted, each muscle fiber that shows any amount of dystrophin is counted as positive in IHC, regardless of the actual quantity of dystrophin present.

As noted above, Study 301 is an ongoing study. For purposes of its review of the NDA, CDER requested that Sarepta perform Western blot analysis on samples obtained from 13 patients enrolled in the study.²⁶ The analysis compared paired biceps samples: baseline samples and samples obtained at 48 weeks, after 48 weeks of treatment with 30 mg/kg of eteplirsen infusion.²⁷ Dr. Woodcock told the SDR Board that representatives from CDER were present in the laboratory for the Western blot analysis and oversaw the procedures and controls. The Western blot analysis showed a statistically significant increase in dystrophin, ranging in an increase from 0.22% to 0.32% of normal.²⁸ It should be noted, however, that a statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit, which is the issue at the core of Drs. Unger and Woodcock’s scientific disagreement.

¹⁸ That is, with respect to time points of assessment and the 2 doses tested.

¹⁹ Appeal at 8-9. Of note, in her decisional memorandum, Dr. Woodcock rejected the findings in both the original and second evaluation of the images: “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.” (Woodcock Decisional Memorandum at 2). She explained to the SDR Board that, after consultation with others in CDER, she does not view IHC results standing alone as a valid method to evaluate dystrophin levels.

²⁰ Appeal at 5.

²¹ *Id.* at 5, 9.

²² *Id.* at 5. Dr. Unger clarifies in his decisional memorandum that the baseline biopsies were from the biceps muscle, the Week 180 biopsies from the deltoid muscle. (Unger Decisional Memorandum at 17).

²³ Appeal at 9. As discussed below, however, Dr. Unger does not believe that those results are reliable.

²⁴ *Id.* at 5.

²⁵ *Id.* at 9-10.

²⁶ *Id.* at 6. Dr. Unger states that the biopsies were obtained from 13 patients but only reports the data as to 12 patients. “There was one patient for whom none of the values met the acceptance criteria [for the Western blot assay].” (Unger Decisional Memorandum at 21).

²⁷ Appeal at 6.

²⁸ *Id.*

2. *Legal Standard for Accelerated Approval and Patient Perspectives*

On December 11, 1992, on the basis of its broad statutory authority to approve drugs under the FD&C Act, FDA issued regulations providing for accelerated approval of drugs.²⁹ Under 21 CFR § 314.510, FDA may grant accelerated approval for a drug based on a surrogate endpoint under certain circumstances:

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on **a surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.³⁰

The preamble to the proposed rule defines “surrogate endpoint” as follows:

A surrogate endpoint, or “marker,” is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.³¹

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 901 of FDASIA amended the FD&C Act to provide FDA with specific authority to grant accelerated approval to drugs for serious conditions.³² Section 506(c) of the FD&C Act now largely tracks language in the regulations issued by FDA in 1992. Section 901 of FDASIA also added current section 506(e) to the FD&C Act, which clarifies that the amendments were “intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval” but that “[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d) of [the FD&C Act].”³³

Section 901 of FDASIA also directed FDA to issue guidance to industry on the development of

²⁹ 57 Fed. Reg. 58942 (Dec. 11, 1992).

³⁰ Emphasis added.

³¹ 57 Fed. Reg. 13234, 13235 (Apr. 15, 1992).

³² FDASIA, PL 112-144, July 9, 2012, 126 Stat. 993.

³³ *Id.*

drugs for accelerated approval and required consideration of the following:

In developing the guidance . . . [FDA] shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.³⁴

Section 1137 of FDASIA further directs FDA to:

develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.³⁵

In May 2014, FDA finalized a guidance on “Expedited Programs for Serious Conditions — Drugs and Biologics.” The Guidance provides general information on the evidence that the agency considers in determining whether to grant accelerated approval.³⁶ The Guidance clarifies that assessing a surrogate endpoint hinges on understanding both the disease process and the relationship between the drug’s effect and the disease process.³⁷ With respect to the latter, the Guidance states:

The extent to which a drug’s effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically[,] but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome.³⁸

The Guidance also provides some insight on how the agency exercises its judgment in evaluating surrogate endpoints when little is known about how an effect on a surrogate endpoint might affect clinical endpoints:

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.³⁹

³⁴ *Id.*

³⁵ *Id.*

³⁶ Expedited Programs Guidance at 19-22.

³⁷ *Id.* at 20-22.

³⁸ *Id.* at 21.

³⁹ *Id.* at 21-22.

FDA obtains patient perspectives through a variety of avenues, “such as open public hearings on specific diseases or drug development issues, and as speakers at FDA-sponsored conferences and workshops.”⁴⁰

3. *SDR-SMG and CDER’s SDR-SOPs*

The Office of the Commissioner issued the SDR-SMG on January 13, 2009. Its stated purpose is “to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency.”⁴¹ The SMG “encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders” and cautions that the “agency’s appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.”⁴² As noted above, the SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals. Under the SDR-SMG, the SDR Board evaluates whether “the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”⁴³ As Chair of the SDR Board, the Chief Scientist then provides a written recommendation on those issues to the Commissioner, who renders a final decision on whether the scientific dispute should be remanded to the Center for further action.⁴⁴

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency’s “requirements for the minimum standards for scientific dispute resolution processes in the Centers” and provides a collection of non-mandatory “best practice[s]” for such dispute resolution.⁴⁵ The SDR-SMG’s requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.⁴⁶

The SDR-SMG then goes on to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes (SDR-SOPs) in the event that such informal attempts at resolution are unsuccessful.⁴⁷ In contrast to the procedural review contemplated by

⁴⁰ 79 Fed. Reg. 65410, 65411 (Nov. 4, 2014).

⁴¹ SDR-SMG at 1.

⁴² *Id.* at 2.

⁴³ *Id.* at 12.

⁴⁴ *Id.* at 12-13.

⁴⁵ *Id.* at 2-3.

⁴⁶ *Id.* at 6.

⁴⁷ *Id.*

the SDR-SMG, Center-level SDR-SOPs should provide for substantive review of the scientific disputes at issue within the Center.⁴⁸

At CDER, there are three interrelated chapters of the Center's Manual of Policies and Procedures (MAPPs) that serve to implement the SDR-SMG's requirements. The first, MAPP 4151.8, "Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions," sets forth CDER's principles for resolving scientific disputes informally and requires "a collaborative environment for decision-making."⁴⁹ According to the MAPP, "[s]uch an environment requires open communication and exchange of ideas in a mutually respectful professional environment[] and the full and open participation of all relevant disciplines and organizational components in the decision-making process."⁵⁰ MAPP 4151.8 states that "[e]ach individual who contributes to the decision-making process" must "be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component" and that "[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made."⁵¹

The second and third MAPPs at issue directly relate to CDER's formal SDR process. MAPP 4151.1, "Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain," provides for raising a scientific issue to the "Next Highest Management Official" (NHMO) if alignment on an issue cannot be reached by the staff on a team or through discussions with a team leader or first-level supervisor. The individual who disagrees with the decision (the disputant) ". . . may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees . . . as well as the proposed changes and rationale for the changes in recommendations and/or conclusions."⁵²

The disputant submits the statement to the NHMO, i.e., "the management official one level above the management official who made the decision being disputed."⁵³ The NHMO then issues a written decision on the issue, and any disputant may then appeal the written decision up the chain of command all the way to the Center Director through use of the same process.⁵⁴ MAPP 4151.2, "Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director," provides for further formal review under certain circumstances if alignment cannot be reached under the process in MAPP 4151.1.⁵⁵ A CDER employee may initiate the process by submitting a written package, which must include "[a]n assessment of the possible significant negative consequences to the public health" at issue in the dispute, to the CDER Ombudsman.⁵⁶ The CDER Ombudsman and the Center Director then "determine whether the consequences of the decision in question are potentially serious enough to warrant" additional review.⁵⁷ If so, the Center Director appoints a chairperson to lead an *Ad Hoc* review panel for purposes of evaluating the scientific dispute and providing a recommendation to the Center

⁴⁸ See *id.*; see also footnote 136.

⁴⁹ MAPP 4151.8 at 2.

⁵⁰ *Id.*

⁵¹ *Id.* at 2-3.

⁵² MAPP 4151.1 at 3.

⁵³ *Id.*

⁵⁴ *Id.* at 4.

⁵⁵ *Id.* at 5; MAPP 4151.2 at 1-2.

⁵⁶ MAPP 4151.2 at 5.

⁵⁷ *Id.*; see also *id.* ("In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted . . .").

Director, who renders the final decision.⁵⁸ The *Ad Hoc* panel typically includes one member with relevant technical expertise, one member chosen from a list provided by the person requesting review, and, if possible, one member with relevant expertise who is external to the agency.⁵⁹

4. *Procedural History of the Dispute in CDER*

Sarepta submitted its NDA for eteplirsen (#206488) on June 26, 2015.⁶⁰ CDER assigned it for review to the Division of Neurology Products (DNP) within ODE-I, the office for which Dr. Unger serves as Director.⁶¹ Even before submission of the NDA, however, representatives from the Office of New Drugs (OND), DNP and ODE-I (the review team) regularly briefed Dr. Woodcock on issues related to the ongoing study of eteplirsen pursuant to an investigational new drug application (IND) and the anticipated NDA.⁶² The discussions at these briefings included among their topics: the suitability of eteplirsen for accelerated approval, an overview and background for eteplirsen, study design, a clinical site inspection report for Sarepta, general brainstorming, and planned communications.⁶³ Dr. Unger told the SDR Board both that there were far more briefings of the Center Director than is typical and that the scope of those briefings included an unusual level of detailed discussion.

During the SDR Board's separate interviews of Dr. Unger and the review team member (RTM), the SDR Board learned that, at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions—anywhere from six to twelve times—from very early on in the review process. The RTM described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as “intense,” “personal,” and “intimidating.” Dr. Unger and the RTM both thought that Dr. Woodcock's early interest and involvement in DNP's approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community in relation to an article published about the initial findings for Study 201/202, which Drs. Unger and Woodcock now agree are misleading and unreliable. Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that OND has been very conservative in evaluating drugs for accelerated approval. In his decisional memorandum, Dr. Unger explains the excitement surrounding eteplirsen at the time as follows:

[The initial findings for Study 201/202] were substantially reported in a 2013 publication, which claimed that eteplirsen markedly increased functional dystrophin production: “...the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43%

⁵⁸ *Id.* at 6-7.

⁵⁹ *Id.* at 6.

⁶⁰ Unger Decisional Memorandum at 1.

⁶¹ *Id.* at 2.

⁶² Appeal at 24-25; Chronology prepared by Virginia Behr and submitted to the SDR Board (Behr Chronology) at 1-2. In his appeal, Dr. Unger consistently refers to the representatives from OND, OND-I and DNP who were involved in the review of the eteplirsen NDA as the “review team” or as “the division,” even though he appears to be referring to senior management within OND on occasion. Dr. Woodcock has also used the same terminology on occasion, though not as consistently. For the sake of efficiency, this memorandum refers to everyone at CDER who was involved in the review of the eteplirsen NDA, besides Dr. Woodcock herself, as the review team. Nonetheless, the SDR Board notes that, within FDA, “review team” is often used to reflect the core team of individuals within a division who are directly engaged in the review of the science underlying a regulatory submission.

⁶³ Appeal at 24-25; Behr Chronology at 1-2.

in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

Publication of this paper was followed by a Sarepta press release, which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community.⁶⁴

In their interviews with the SDR Board, Dr. Unger and Dr. Woodcock stated that FDA also received significant correspondence from the public and Congress, much of which urged approval of eteplirsen.⁶⁵ Some of the correspondence used vulgar language and was abusive to the review staff.⁶⁶

The briefings of Dr. Woodcock began again five to six months after submission of the NDA for eteplirsen.⁶⁷ The focus of these briefings was on preparation for a planned meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC meeting) to provide advice on the review of the eteplirsen NDA, which meeting was initially scheduled for January 2016 but then rescheduled for April 25, 2016.⁶⁸ The preparation involved discussions of the ongoing review of the data, including the “strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.”⁶⁹ During their respective interviews with the SDR Board, both Dr. Unger and the RTM conveyed their belief that Dr. Woodcock was inclined to grant approval from very early on in the process. But the RTM stated that Dr. Woodcock’s views were not always clear during discussions throughout the review of the science—sometimes she seemed to agree with external constituents, sometimes not. The RTM told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged DNP to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases). The RTM highlighted to the SDR Board that at least two members of the review team were leaving FDA or had left the agency in the wake of both the decision-making process within CDER and the pressures exerted by outside forces.

Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014. She said that her goal throughout the discussions

⁶⁴ Unger Decisional Memorandum at 11 (emphasis in original), citing Mendell JR, *et al*: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47 and Sarepta press release, dated 8/8/13 (<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irolnewsArticle&ID=1846052>). Dr. Unger also notes, “It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible.” Unger Decisional Memorandum at 11.

⁶⁵ See also Appeal at 23.

⁶⁶ See, e.g., *id.* at 23-24.

⁶⁷ *Id.* at 25; Behr Chronology at 2-3.

⁶⁸ Appeal at 25; Behr Chronology at 2-3.

⁶⁹ Appeal at 25.

with the review team was to convince them to come around to her more flexible way of thinking about the data. According to Dr. Woodcock, she recognized that there were serious and significant flaws in the study design for Study 201/202 and the data it generated but that she did not “want to hold” those flaws “against the patients.” She conceded that the results produced by Studies 201/202 and 301 were always less than anyone in CDER had hoped.

In their respective interviews with the SDR Board, both Dr. Unger and the RTM focused to some extent on Dr. Woodcock’s involvement in the planning stages for the AC meeting. They expressed some surprise at the extent of her involvement. Dr. Unger indicated in his interview with the SDR Board that Dr. Woodcock even advocated, unsuccessfully, for changing the order of the questions to be posed to the committee and wanted the question on conventional approval to come before the one on accelerated approval.

The RTM told the SDR Board: (1) that Dr. Woodcock made it clear in one or more of the meetings leading up to the AC meeting that she intended to speak at the meeting but (2) that the substance and purpose of her participation were never communicated. Although the RTM affirmatively stated that the review team was free to develop its own presentation to the committee, uncertainty with respect to Dr. Woodcock’s role made doing so more difficult. The RTM also noted that Dr. Woodcock requested a longer than is typical Open Public Hearing portion of the AC meeting that, as a result, the review team thought there would insufficient time for them to make their presentations during a one-day meeting. The RTM stated that the review team asked to extend the advisory committee to two days but that they were overruled.

On April 25, 2016, CDER held the AC meeting. The meeting focused on the data from Study 201/202.⁷⁰ Dr. Woodcock spoke at the meeting several times. At the meeting she made a presentation that was intended to “provide a framework within which to consider [the] data [underlying the eteplirsen NDA] based on [her] 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval.”⁷¹ She highlighted many of the difficulties in interpreting the data.⁷²

At the AC meeting, Dr. Woodcock also described the standards for both conventional and accelerated approval of drugs but mentioned that the agency had not “articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit.”⁷³ She concluded her presentation with the following remarks:

I would note that much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective.

There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally [] have little say in how the standards are implemented.

The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you’ve heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent

⁷⁰ Sarepta had not yet submitted the data from Study 301.

⁷¹ Advisory Committee Transcript at 151.

⁷² *Id.* at 151-155.

⁷³ *Id.* at 155-156.

presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated initially and that in fact sometimes we will collectively get it wrong, otherwise accelerated approval would really have no different standards than regular approval.⁷⁴

During the questions to the committee members, Dr. Woodcock restated the standard for accelerated approval and emphasized that, with regard to the surrogate endpoint of dystrophin, there has never been a “threshold established [to show a reasonable likelihood of predicting clinical benefit] because there's never been a drug to do this.”⁷⁵ When later asked for clarification of the extent to which the committee members were to incorporate the testimony of the boys and their families into their evaluation of clinical outcomes for Study 201/202, Dr. Woodcock stated:

Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk. * * * So the statutory standard is more or less as described there, but there is flexibility, and that's where we should take the views of the community into account.⁷⁶

During his SDR Board interview, the RTM stated that, notwithstanding Dr. Woodcock's emphasis on accelerated approval and the standard of “reasonably likely to predict clinical benefit,” “[s]urrogacy was not discussed in any genuine scientific way” during the AC meeting because it had not been framed that way by Sarepta through its presentation to the committee. The RTM specifically stated that there was no discussion of “substantial evidence” in the context of accelerated approval, nor what might constitute “interpretable evidence.” The RTM believed that, by the end of an emotional AC meeting, the framework for evaluating the data under the appropriate regulatory standards, as provided by the review team toward the start of the meeting, had been forgotten by the committee members.

Dr. Woodcock explained to the SDR Board that she thought both that the review team did a poor job framing the issues during their presentations and that the questions were confusing and poorly worded. Indeed, during her interview with the SDR Board, Dr. Woodcock opined that the review team “did not put its best foot forward.” She speculated that the confounding factor was the number of interested persons attending both in person and by webcast. She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen. She thought that the review team's presentation of the IHC data, in particular, was confusing. She further opined that the review team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand. Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates.

At the conclusion of the AC meeting, the committee voted against accelerated approval by a margin of 7-6.⁷⁷ Three of the members who voted in favor of accelerated approval were the consumer representative and the two patient representatives.⁷⁸

⁷⁴ *Id.* at 158-59.

⁷⁵ *Id.* at 484.

⁷⁶ *Id.* at 548-549.

⁷⁷ *Id.* at 486-95.

⁷⁸ *Id.* at 2-7, 486-88.

On May 4, 2016, Dr. Woodcock met with the review team to discuss the AC meeting and plan of actions for the NDA.⁷⁹ In his appeal, Dr. Unger contends that Dr. Woodcock “made clear her intent to approve the drug” at this meeting, even though she had not yet reviewed drafts of DNP’s final review memorandum or his review memorandum.⁸⁰ According to Dr. Unger, Dr. Woodcock explained that she had already “reached a different conclusion” than the review team.⁸¹ Dr. Woodcock explained to the SDR Board that the memoranda were discussed during the Center Director briefings and that she felt she understood the views of the review team and did not see the point of an “exchange of reviews.”

On May 24, 2016, Dr. Unger met privately with Dr. Woodcock to discuss the eteplirsén decision.⁸² On May 31, 2016, Dr. Woodcock met with representatives from the review team to discuss their reviews and her initial draft of a decisional memorandum based primarily on the data from Study 201/202.⁸³ Dr. Woodcock received comments back from the review team at the same meeting.⁸⁴ Dr. Unger told the SDR Board that he and members of the review team—including Dr. Robert Temple, Deputy Center Director for Clinical Science and Dr. John Jenkins, Director of OND—discouraged Dr. Woodcock from finalizing the decisional memorandum and granting accelerated approval for eteplirsén until the additional data from Study 301 could be obtained.

On June 3, 2016, in response to an email from Sarepta, a letter signed by Dr. Woodcock issued to the sponsor.⁸⁵ The letter requested the additional data from Study 301, which was to include comparisons of any biopsy samples obtained at Week 48 to the respective baseline samples for those patients.⁸⁶ The letter stated,

If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).⁸⁷

Dr. Woodcock explained that Dr. Unger and the review team essentially agreed to the timeframe of four business days, though they pushed instead for six. She felt that there was general agreement that data from only twelve patients could be reviewed quickly, especially given that representatives from CDER would be overseeing the Western blot analysis and ensuring that it was done properly.

On June 27, 2016, Sarepta submitted the requested data.⁸⁸ Dr. Woodcock explained that accelerated approval was not granted within four business days of that date precisely because the results of the analysis were disappointing in that they provided evidence of only a minimal increase in dystrophin at 48 weeks. Dr. Unger sent an email to Dr. Woodcock that read:

⁷⁹ Appeal at 25; Behr Chronology at 2.

⁸⁰ Appeal at 26.

⁸¹ *Id.*

⁸² Behr Chronology at 2.

⁸³ Appeal at 26; Behr Chronology at 2.

⁸⁴ Behr Chronology at 2.

⁸⁵ June 3, 2016, General Advice letter.

⁸⁶ *Id.* at 1.

⁸⁷ *Id.* at 1-2.

⁸⁸ Unger email to the SDR Board, dated July 22, 2016.

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-1. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.⁸⁹

On July 6, 2016, Dr. Woodcock met with the review team one final time.⁹⁰ During the meeting, Dr. Woodcock "indicated to the review team that [she] had read their memoranda that had been updated to reflect the new [Western blot] data, and that [she] maintained [her] position that the application should receive accelerated approval based on dystrophin production."⁹¹ She discussed her rationale, which—based on her notes—appears to have tracked the rationale in her final decisional memorandum.⁹²

On July 8, 2016, in light of Dr. Unger's stated intention of filing an appeal with the Office of the Commissioner, Virginia Behr, CDER Ombudsman, began working with him and Dr. Woodcock to determine whether the institution of any formal appeals under CDER's SDR-SOPs was warranted.⁹³ Ms. Behr had determined that the procedure outlined in MAPP 4151.1,

⁸⁹ Unger email dated July 5, 2016.

⁹⁰ Appeal at 26; Behr Chronology at 3.

⁹¹ Woodcock's handwritten notes, dated July 6, 2016, at 1.

⁹² *Id.* at 2. Also of note, on July 7, 2016, Dr. Unger briefed you on his rationale for disagreeing with Dr. Woodcock's underlying scientific reasoning for granting accelerated approval for eteplirsen (Behr Chronology at 3).

⁹³ See "Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection" (SDR-SOPs Agreement).

“Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain” did not apply because the disagreement was between the Center Director and a subordinate two levels below her.⁹⁴ She also questioned the utility of using MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.”⁹⁵ She reasoned that “the CDER Director ha[d] already fully evaluated the issues and [was] one of the parties involved in the dispute” and that “utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”⁹⁶ She nonetheless consulted with both Drs. Unger and Woodcock, who both agreed to bypass the *Ad Hoc* panel process in favor of the process outlined in the SDR-SMG.⁹⁷ During his presentation to the SDR Board, Dr. Unger also indicated that he thinks referring the matter to an *Ad Hoc* panel would have been pointless because Dr. Woodcock had already made up her mind and a new process would not have changed the outcome.

On July 11, 2016, Dr. Woodcock provided a draft of her final decisional memorandum to the review team.⁹⁸ She received comments back from Dr. Unger; Dr. Jenkins, the Director of OND; and Dr. Ashutosh Rao, of the Office of Biotechnology Products, who was also on the review team.⁹⁹ The comments from Drs. Unger and Rao do not debate the action proposed in Dr. Woodcock’s draft decisional memorandum or its underlying scientific conclusions.¹⁰⁰ Instead, they focus on clarifying certain facts asserted in the memorandum, and Dr. Unger provided information regarding the clinical course of 11 patients enrolled in Study 201/202 to 240 weeks.¹⁰¹ Dr. Jenkins provided more detailed analysis on and critique of some of Dr. Woodcock’s findings and he expressed concern about her conclusions. However, he made no attempt in his written comments to dissuade her from her ultimate conclusion regarding accelerated approval.¹⁰² By email on the afternoon of July 13, Dr. Unger stated, “I’ve canvassed the Division, and we have no additional comments.”¹⁰³ Dr. Unger told the SDR Board that he and the review team understood that Dr. Woodcock had already made up her mind and that thus they did not see a point in criticizing Dr. Woodcock’s draft decisional memorandum.

Furthermore, the RTM told the SDR Board that some of the positions taken by Dr. Woodcock in the draft decisional memorandum were brand new to him but that he did not feel any feedback he could provide would receive due consideration by Dr. Woodcock. The RTM expressed concern that Dr. Woodcock’s analysis for “reasonably likely to predict clinical benefit” raised new issues and information that should have been presented at the beginning of the review and that had not been addressed by the review team or, perhaps more importantly, presented by the sponsor in support of the NDA. The RTM specifically discussed with the SDR Board the section of the finalized version of the memorandum addressing whether the data for eteplirsen is adequate to show a reasonable likelihood of predicting clinical benefit.¹⁰⁴ As an example of his concerns, the RTM pointed to section (B)(5) of the decisional memorandum, which details the findings in the

⁹⁴ *Id.* at 1. It is also clear from the record before the SDR Board that the supervisor between Drs. Unger and Woodcock, Dr. John Jenkins, agreed with Dr. Unger.

⁹⁵ *Id.*

⁹⁶ *Id.* at 2.

⁹⁷ *Id.*

⁹⁸ Behr Chronology at 3.

⁹⁹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); Jenkins email dated July 12, 2016; and emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰⁰ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰¹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰² Jenkins email dated July 12, 2016.

¹⁰³ Unger email dated July 13, 2016 and sent at 3:19 PM.

¹⁰⁴ Woodcock Decisional Memorandum at 5-10.

scientific literature regarding “the relationship of dystrophin expression to clinical status.”¹⁰⁵ The RTM indicated that he or she knows the scientific literature at issue very well and that he or she could have provided significant input into the evaluation of the literature and the underlying data and analysis. The RTM conveyed that he did not do so because he felt Dr. Woodcock had already made her decision.

On July 14, 2016, Dr. Woodcock finalized her decisional memorandum. She explained to the SDR Board that her conclusion regarding whether the increase in dystrophin production identified by Studies 202 and 301 was reasonably likely to predict clinical benefit was based on her own “medical/scientific judgment.” She emphasized that she has thirty years of experience at FDA and that she has far more experience in assessing this type of evidence for an “ultra-rare rare” disease than the review team. She thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case. Her stated goal for the decisional process was to move the review team toward what she viewed as a more reasonable approach. She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to “sure bet” drugs and that confirmatory trials are required for a reason. Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval. She also criticized OND for not issuing clear guidance on what constitutes a sufficient drug effect to be “reasonably likely to predict clinical benefit,” as she had suggested for an extended period of time. She also thought that the review team’s views on balancing the mean results of a clinical study with a targeted evaluation of responsive patients were misplaced, particularly in a DMD population, where additional genetic mutations or deficiencies could have a profound effect on the outcome.

In her presentation to the SDR Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

On July 16, 2016, Dr. Unger finalized his own decisional memorandum. In her own decisional memorandum, dated July 14, 2016, Dr. Woodcock indicated that she had read Dr. Unger’s decisional memorandum,¹⁰⁶ although she could not have done so given the timing of the two memoranda. She explained to the SDR Board that she did not feel she needed to see a finalized version of Dr. Unger’s decisional memorandum because she was already familiar with his views on the data and the decision. She also stated that there was nothing in Dr. Unger’s appeal, which is based largely on his finalized decisional memorandum, that would have changed her mind on her decision or the underlying rationale. She stated, “He is entitled to his own opinion.”

5. Dr. Unger’s SDR Appeal

In his appeal, Dr. Unger focuses his arguments almost exclusively on the substance of his scientific disagreement with Dr. Woodcock. Indeed, Dr. Unger makes clear in his appeal that he

¹⁰⁵ *Id.* at 7-10.

¹⁰⁶ *Id.* at 1.

seeks “a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit.”¹⁰⁷ Insofar as he explicitly addresses potential procedural issues under the review process contemplated by the SDR-SMG, he does so in two paragraphs toward the end of the appeal.¹⁰⁸ He first states that Dr. Woodcock’s “direct involvement with this drug, compared to other development programs, has been unprecedented.”¹⁰⁹ He states further that “[s]he also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.”¹¹⁰ After conceding that “[t]here is no question that there has been adequate time and place for the discussion of various views,” Dr. Unger notes that he found it unfortunate that “the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division’s final review memorandum or my review memorandum.”¹¹¹ As noted above, Dr. Unger indicates that Dr. Woodcock conveyed that she had “already ‘. . . reached a different conclusion . . .’ than the review team.”¹¹²

In his presentation to the SDR Board, Dr. Unger highlighted that Dr. Woodcock had never seen the charts on page 10 of his appeal. Those charts show: (1) a comparison of the *original* IHC results for baseline samples in the three patients whose biopsies were available at 180 weeks to the IHC results for those same samples when they were re-evaluated after 180 weeks and (2) a comparison of the IHC and the Western blot results at 180 weeks.¹¹³ Dr. Unger stated, however, that those charts were consistent with his earlier positions and would likely not affect Dr. Woodcock’s analysis or decision. In a follow-up email to the SDR Board, Dr. Unger also contended that Dr. Woodcock diverted from protocol when she finalized her decisional memorandum on July 14, 2016, two days before his.

In his appeal, Dr. Unger frames his scientific disagreement with Dr. Woodcock as follows: “The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit.”¹¹⁴ Nonetheless, Dr. Unger explains his disagreement with Dr. Woodcock through multiple challenges to the reliability of the underlying data and specific issues he has with her rationale or the evidentiary basis for such rationale. Of note, he makes the following scientific arguments:

- As noted above, Study 201 showed only “a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group...”;¹¹⁵
- Study 201/202 was fundamentally flawed in several respects:
 - “[T]he baseline biopsies were obtained from [external controls] . . . who could differ in unknown ways from the subjects in Study 201/202”;¹¹⁶
 - “[T]he Week 180 biopsies were obtained from different muscles than the baseline biopsies”;¹¹⁷ and

¹⁰⁷ Appeal at 26.

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.* at 10.

¹¹⁴ *Id.* at 3.

¹¹⁵ *Id.* at 9.

¹¹⁶ *Id.* at 5.

¹¹⁷ *Id.*

- “The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline....”¹¹⁸
- Although the available data generated by Study 301 were the product of an adequate and well-controlled study and showed a statistically significant increase of dystrophin, the drug effect (i.e., an increase from 0.22% to 0.32% of normal) is not reasonably likely to predict clinical benefit.¹¹⁹
 - “The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications”;¹²⁰
 - “Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that ‘...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.’ She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit”;¹²¹ and
 - “No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.”¹²²

He also makes several overarching policy and legal arguments that call into question the appropriateness of Dr. Woodcock’s decisional memorandum. His key arguments focus on the effects that Dr. Woodcock’s decision would have on the pathway for accelerated approval and the standard for “reasonably likely to predict clinical benefit.”¹²³ He also highlights the negative effects that accelerated approval would have on the patients themselves, including false hope, abandonment of other therapies, and a decline in drug development for DMD.¹²⁴ He further questions “the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic[] when the consequence of a sub-therapeutic dose is clinical deterioration and death.”¹²⁵ Finally he worries that approving eteplirsen based on the data submitted by the sponsor “would send the signal that political pressure and even intimidation—not science—guide[] FDA decisions.”¹²⁶

ANALYSIS

1. *Whether CDER followed its own processes.*

The first issue for the SDR Board to consider is whether CDER followed its own processes in addressing Dr. Unger’s scientific dispute. Dr. Unger does not contend that there were any issues with respect to how CDER chose to address and implement its own formal appeals process under the SDR-SOPs in this case. In his appeal, Dr. Unger points instead to four deviations from typical Center process: (1) Dr. Woodcock’s involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 7.

¹²⁰ *Id.* at 13.

¹²¹ *Id.* at 15.

¹²² *Id.*

¹²³ *Id.* at 21-22.

¹²⁴ *Id.*

¹²⁵ *Id.* at 23; *see also* Unger Review Memorandum at 4, 5.

¹²⁶ *Id.*

in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In its review of the administrative file and the surrounding circumstances, the SDR Board has also identified below other potential deviations from process at the Center level.

The agency-wide SDR-SMG directs the SDR Board to focus on the Center's SDR-SOPs in evaluating whether the Center followed its own processes in evaluating a scientific dispute. In this case, however, both Drs. Unger and Woodcock have agreed that the only applicable SDR-SOP, MAPP 4151.2, provides for a review by the Center Director in consultation with an *Ad Hoc* panel and that going through such a process at this stage would be futile. The SDR Board has determined that, absent the second aspect of that agreement regarding futility and the underlying unusual circumstance of this scientific dispute, there would be reason to refer the matter back to the Center for further review by an *Ad Hoc* panel.

The interplay between MAPP 4151.1 and 4151.2, the former of which provides for supervisory review of scientific disputes all the way to the Center Director, suggests that MAPP 4151.2 actually calls for additional review of a scientific dispute by the Center Director under certain circumstances even if she has already made a decision on the dispute. Although MAPP 4151.2 provides for bypassing review of the scientific dispute up the chain of command under MAPP 4151.1 if such exhaustion would impede the timely resolution of a serious public health issue, MAPP 4151.2 also emphasizes that it should not be used before other means of resolution have been attempted.¹²⁷ However, the key consideration for obtaining review by an *Ad Hoc* panel under MAPP 4151.2 is “whether the consequences of the decision in question are potentially serious enough to warrant [additional review],” not whether the resort to the process would be futile.¹²⁸ It appears that Dr. Woodcock has never made a determination regarding the seriousness of the decision in question, but it would be surprising if she determined that the dispute in this case did not meet the standard, as reflected in the statement she signed.¹²⁹

In this case, however, it is clear from the record before the SDR Board that Dr. Woodcock was so involved in the underlying scientific dispute—including direct and extensive personal review of the data and analyses offered in support of the NDA—that we agree with the conclusion in the agreements signed by Drs. Unger and Woodcock that “the CDER Director has already fully evaluated the issues.”¹³⁰ Indeed, she has already received advice from an advisory committee and had substantial conversations with her staff over an extended period of time with respect to the dispute in question. There is no reason to believe that receiving additional advice from an *Ad Hoc* panel would alter Dr. Woodcock's views of the scientific issues. As the agreement between her and Dr. Unger reflects, the process would be time-consuming and delay an important

¹²⁷ MAPP 4151.2 at 5. (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a [request for review under 4151.2] is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include . . . a written request to bypass these other mechanisms. . . .”).

¹²⁸ *Id.*

¹²⁹ SDR-SOPs Agreement at 2 (“The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.”).

¹³⁰ *Id.*

regulatory decision unnecessarily.¹³¹ Dr. Unger also told the SDR Board that he thought going through the *Ad Hoc* panel process would have been pointless for the aforementioned reasons.

The difficulty for the SDR Board is that the agency-wide SDR-SMG is predicated on some level of formal scientific dispute resolution within the Center, particularly a decision by the Center Director regarding the formalized scientific dispute.¹³² For that reason, the focus of the SDR-SMG with respect to the process followed is on whether the Center followed its own SDR-SOPs in resolving the scientific dispute.¹³³ Yet, the SDR-SMG also directs the Centers to adopt “[i]nformal methods” for resolving scientific disputes, “to create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” to use “good management practices for resolving conflict,” and “to enable as open and complete a discussion of the issues as possible at the working level of the organization.”¹³⁴ As a result, the SDR Board has determined that reviewing the processes used by a Center to resolve a scientific disagreement is appropriate under the SDR-SMG even when, as here, the initiator has not availed himself of the Center’s formal process for resolving scientific disputes and the Center Director has explicitly agreed to that approach.

Whether the Center followed its own processes for resolving a scientific disagreement cannot be viewed in a vacuum, however. Indeed, the SDR-SMG itself—at its most concise and in its clearest voice—states, “The goal of [the SDR Board’s] review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”¹³⁵ Particularly in the context of a scientific dispute that did not go through a formal SDR process at the Center but nonetheless received extensive review by the Center Director, focusing on deviations from process without any regard to whether they affected the initiator’s opportunity to present his views of the science (and to some extent whether those views and the evidence were considered) would seem to miss the point of that review. Accordingly, the SDR Board finds that it is more appropriate to address Dr. Unger’s arguments regarding the Center’s deviations from appropriate process under the second prong of its analysis: whether the Center provided Dr. Unger an adequate opportunity present his scientific concerns.

The SDR Board’s one caveat is that, as noted above, the SDR-SMG does appear to assume that there has been both at least some use of the formal dispute resolution within the Center and, accordingly, a *formal* substantive review of the initiator’s scientific concerns before reaching the Office of the Commissioner.¹³⁶ The limited scope of the SDR Board’s review under the SDR-SMG—i.e., an evaluation of the Center’s decision-making process—means that Dr. Unger will also not receive a substantive review of his scientific concerns under the SDR-SMG. In fact, at the conclusion of the SDR Board’s review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level. Particularly in light of

¹³¹ *Id.* (“[U]tilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”).

¹³² *See* SDR-SMG at 6 (requiring as a mandatory process for formal scientific dispute resolution a written opinion by the Center Director and stating that such a written opinion as a step in the process is a “central criterion for advancement to the agency-level appeals process.”).

¹³³ *See, e.g., id.* at 12 (requiring the SDR Board to “obtain the full administrative record of the Center’s processes for the dispute and review the Center’s published SOP(s)” and to “review that information to determine whether written Center processes were followed.”).

¹³⁴ *Id.* at 6.

¹³⁵ *Id.* at 12.

¹³⁶ *See id.* at 6 (referring to SOPs for resolution of Center-level scientific disputes without limiting them to procedural reviews and contemplating the Center SOPs as a continuation of the informal SDR process).

Dr. Unger's explicit request for scientific review of the matter within the Office of the Commissioner, therefore, the SDR Board recommends additional substantive review at this level, as is discussed below.

2. *Whether CDER provided an adequate opportunity to Dr. Unger to present his scientific concerns.*

In his appeal, Dr. Unger admits, "There is no question that there has been adequate time and place for the discussion of various views."¹³⁷ In so doing, he appears to concede away most of his arguments with respect to whether he had an adequate opportunity to present his scientific concerns, notwithstanding the procedural deviations he identifies. The SDR Board, however, has not taken Dr. Unger's concession at face value and has instead looked beyond it to evaluate the administrative file and the surrounding circumstances to identify additional procedural issues. We conclude nonetheless that Dr. Unger had an adequate opportunity to present his scientific concerns to Dr. Woodcock before she issued her decisional memorandum.

As noted above, Dr. Unger identified four deviations from Center's typical decision-making process for the eteplirsen NDA: (1) Dr. Woodcock's involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In reviewing this matter, the SDR Board—which includes among its members Ombudsmen from other Centers that oversee reviews of medical products—also considered other departures from the typical processes used by Centers in reviewing applications for pre-market approval or clearance.¹³⁸

The SDR Board agrees with Dr. Unger that it was unusual for a Center Director to be so involved in the early stages of reviewing an NDA, but the consensus on the SDR Board was that Dr. Woodcock went several steps further than mere involvement and thereby departed from typical practice among the Centers. By her own admission, Dr. Woodcock had a direct hand in reviewing the data submitted in support of the NDA, even before the review team had written their draft review memoranda, and actively encouraged the review team—including Dr. Unger—to come around to her way of thinking in their own reviews. Specifically, she wanted the review team to agree with her that the limited increase in dystrophin production established by the data in Studies 201/202 was sufficient to show a reasonable likelihood of predicting clinical benefit. At several points during the decision-making process for what is clearly a critical scientific issue for the agency, Dr. Woodcock also provided a very limited amount of time for Dr. Unger and the review team to provide feedback on additional data or her own scientific conclusions—most notably when Sarepta submitted the data from Study 301 and when she provided two separate draft versions of her decisional memorandum to the review team.

Notwithstanding the foregoing procedural shortcomings, the SDR Board finds that Dr. Unger had an adequate opportunity to present his scientific views. Not only does he admit in his appeal that he had an opportunity, but the record before the SDR Board demonstrates that he did. He and the rest of the review team met with Dr. Woodcock on multiple occasions both before and after the AC meeting. Drs. Unger and Woodcock both told the SDR Board that those meetings involved substantive and detailed discussions of the data and science and the appropriate

¹³⁷ Appeal at 26.

¹³⁸ See SDR-SMG at 3 (defining the SDR Board to include Ombudsmen from all of the Centers).

conclusions to be drawn from them. Although Dr. Unger complains that Dr. Woodcock was involved in aspects of the NDA that went far beyond the norm for a Center Director at CDER, including her role in the AC meeting, and that she reached or finalized decisions before reviewing review or decisional memoranda, he does not maintain that those procedural deficiencies compromised his ability to present his views. In fact, his own final decisional memorandum—which Dr. Woodcock apparently saw in draft form before she finalized her own—discloses that he felt empowered to push back on both Dr. Woodcock’s scientific conclusions and their basis, despite the fact that he believed his efforts would be futile. Indeed, he conceded to the SDR Board that nothing in his decisional memorandum or appeal submission would have affected Dr. Woodcock’s decision on the scientific issue in question (including the charts that he created for the first time in preparing his appeal submission under the agency-wide SDR-SMG). He further conceded as much when he agreed not to pursue further review through the *Ad Hoc* panel process under CDER’s SDR-SOPs. In short, through his own perseverance, confidence in his own scientific expertise, and perhaps dint of personality, Dr. Unger ensured that he himself had an adequate opportunity to present his scientific views despite the procedural irregularities in the decision-making process within CDER.

The SDR Board nonetheless remains concerned about Dr. Woodcock’s extensive involvement in the review of the eteplirsen NDA, including her degree of participation at the AC meeting, and the limited timeframe she provided for feedback on the data from Study 301 and her own scientific conclusions on that data. We fear that those actions could have chilled scientific debate within CDER and reduced the level of participation by the review team during the final stages of the decision-making process. By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement. By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger. Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER’s review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval.

To complicate matters further, Dr. Woodcock subsequently circulated a draft decisional memorandum but provided only a limited amount of time for comments, even though the draft decisional memorandum was the first time some on the review team had apparently seen key elements for the basis of her decision on “reasonably likely to predict clinical benefit.” The response from the review team is telling. As noted above, only Drs. Jenkins and Unger and another reviewer outside of DNP provided comments. Except for Dr. Jenkins, no one made any effort to make substantive comments beyond tips on how to make factual clarifications or to supplement her analysis with additional data. It appears that, because the review team knew Dr. Woodcock’s views by then, they saw no point in providing any additional substantive review or meaningful feedback on any new issues raised by Dr. Woodcock’s memorandum. Indeed, Dr. Unger and the RTM conveyed as much to the SDR Board.

There is no doubt that a Center Director should have wide latitude in leading the direction of the Center in a manner consistent with her priorities and vision. The SDR Board also believes that Center Directors have a role to play not only with respect to the resolution of scientific disputes at issue in individual applications for pre-market-authorization by FDA, as evidenced by both the SDR-SMG and CDER’s own SDR-SOPs, but also with respect to the ultimate decision on

scientific issues that are not the subject of a dispute. It is also clear from Dr. Woodcock's presentation to the SDR Board that she firmly believes in the correctness of her scientific decision in this case and that her involvement in the review of the eteplirsen NDA was always motivated by the best of intentions. However, the SDR Board finds Dr. Woodcock's extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process.

Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had even completed their draft scientific reviews, Dr. Woodcock had told them—on May 4, 2016—that she intended to grant accelerated approval. This sort of top-down review does not, in the SDR Board's view, “create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” as reflected in the SDR-SMG's requirements for resolution of scientific disagreements by the Center.¹³⁹ By the time Dr. Woodcock issued her draft decisional memorandum on what she herself acknowledged was a difficult scientific issue of incredible magnitude for the agency—i.e., whether the evidence regarding dystrophin production was reasonably likely to predict clinical benefit—the review team had decided it was pointless to challenge her ultimate conclusion or its basis.¹⁴⁰ Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.

3. Whether the Center Director considered all relevant evidence bearing on the scientific question at issue.

The third issue for the SDR Board is whether CDER, including Dr. Woodcock, fully considered all relevant evidence in resolving the scientific dispute at issue, i.e., whether the evidence of eteplirsen's effect on dystrophin production is reasonably likely to predict clinical benefit. In this case, both Drs. Unger and Woodcock appear to agree that she *considered* all relevant evidence. As noted above, Dr. Unger does not believe that any additional data or evidence available to him could persuade Dr. Woodcock that she has reached the wrong scientific conclusion. For her part, Dr. Woodcock does not feel that she has disregarded any relevant evidence. Moreover, in her interview with the SDR Board, she demonstrated an awareness and command of all of the evidence weighing against the scientific decision she has made, including the arguments and analysis of the evidence presented in Dr. Unger's appeal.

Whether Dr. Woodcock has *addressed* all of the relevant evidence in her decisional memorandum is a more difficult question. In concluding that the minimal increase in dystrophin

¹³⁹ *Id.* at 6.

¹⁴⁰ In this regard, it is also worth noting again the language quoted above in the background section: “Each individual who contributes to the decision-making process” must “be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component” and that “[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made.” (MAPP 4151.8 at 2-3).

production seen in the data is reasonably likely to predict clinical benefit, Dr. Woodcock has provided a very limited rationale.

At the risk of oversimplification, Dr. Woodcock found, in essence, that the studies attempting to correlate levels of dystrophin with clinical benefit, as have been reported in the scientific literature, are unreliable in this context for variety of reasons, including: (1) the subjectivity of the clinical evaluation, (2) the difficulty in correlating IHC results with Western blot results, (3) the influence of anti-dystrophin antibodies, (4) the lack of information on dystrophin quality (as opposed to quantity) in the different studies, (5) deficiencies in Western blot techniques from earlier studies, and (6) the wide range of findings with respect to the correlation of dystrophin levels with clinical benefit.¹⁴¹ She concluded, therefore, 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,” and that the “biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.”¹⁴² She then attempted to bolster that conclusion with a theory regarding the effect of exon 52 deletion and her reanalysis of the intermediate clinical outcomes for a subset of subjects in Study 201/202.¹⁴³ She further explained to the SDR Board that she was exercising her “medical/scientific judgment” in reaching the scientific conclusion that she did.

It is easy for the SDR Board to understand why Dr. Unger’s appeal expressed such frustration with this explanation of Dr. Woodcock’s rationale. He states:

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients could benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.¹⁴⁴

Of course, *considering* the relevant evidence and *addressing* the relevant evidence in a manner satisfactory to Dr. Unger or the SDR Board are two different propositions. The SDR Board finds, based on the record before us, that Dr. Woodcock has considered all relevant evidence in reaching her scientific conclusion. Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger—both with respect to the scientific conclusion and the sufficiency of the underlying rationale.

4. Whether the dispute should be remanded to the Center Director.

Inasmuch as the SDR Board has concluded that Dr. Unger had an adequate opportunity to present his scientific concerns during the decision-making process at CDER and that Dr. Woodcock considered all relevant evidence in making her decision, the SDR Board does not recommend returning this matter to the Center Director for corrective action. We also believe that, for reasons discussed above, remanding this matter to the Center Director would be futile.

¹⁴¹ Woodcock Decisional Memorandum at 5-9.

¹⁴² *Id.* at 9.

¹⁴³ *Id.* at 10.

¹⁴⁴ Appeal at 20 (emphasis in original).

CONSIDERATIONS FROM THE ACTING CHIEF SCIENTIST

In my capacity as Acting Chief Scientist, I feel the responsibility to convey some comments regarding the underlying science for the decision being challenged by Dr. Unger in his appeal. I cannot begin to understand the depth of pain and suffering that patients with DMD and their families endure. As an experienced physician, I struggle to identify any other diseases associated with this degree of suffering, not only to patients but to their families. Nevertheless, my assessment is that the data presented by the sponsor to date are not adequate to support accelerated approval of eteplirsen

Studies in animals showing that eteplirsen leads to “exon 51 skipping” are an important first step in assessing whether eteplirsen might work for a subset of patients with DMD because skipping exon 51 is necessary for the production of dystrophin in these patients.¹⁴⁵ The next step is to assess whether eteplirsen actually leads to the production of dystrophin in patients with DMD and, if so, whether such an increase in dystrophin confers clinical benefit. Despite the promising animal studies demonstrating exon 51 skipping, both Drs. Woodcock and Unger, as well as the review team in CDER, agree that the amount of dystrophin produced in the clinical studies conducted at doses of up to 50mg/kg per week is very low. Animal data suggest that the doses studied in humans is too low; in animals, exon 51 skipping was detected in a nonlinear, dose-dependent manner (that is, higher doses led to significantly more exon 51 skipping). Specifically, with a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. These dose-dependent responses are important because it is wholly conceivable that higher doses would lead to a much greater amount of dystrophin production, which could be important for clinical benefit. Because the drug appears to be safe, the review team recommended evaluation of much higher doses of eteplirsen, of at least 200mg/kg per week. Approving a drug at a dose that does not show a meaningful increase in dystrophin (when the drug could theoretically achieve one at higher doses) is concerning.

As for accelerated approval, the regulatory standard at issue requires a sponsor to show that the drug under review leads to an effect on the surrogate endpoint (in this case, the production of dystrophin) and that the effect is reasonably likely to predict clinical benefit (in this case, improving, or slowing down decline in, muscle function). The term “reasonably likely to predict” acknowledges the potential for doubt in the outcome of interest. Indeed, nobody knows the minimum level of dystrophin that is likely to confer clinical benefit in patients with DMD. The critical scientific and regulatory issue at stake in CDER’s decision here is whether such minute amounts of dystrophin are reasonably likely to predict clinical benefit at the dosage of the drug subject to approval. In this case, both Drs. Woodcock and Unger have attempted to provide a rationale, based on scientific and professional judgment, for whether or not such small levels of dystrophin are reasonably likely to predict the clinical effect of interest. By any meaningful objective standard, however, the overall evidence derived from eteplirsen’s limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit. As pointed out in Dr. Unger’s appeal, “Study 201 did not show a treatment effect on its 1^o clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients.”¹⁴⁶

¹⁴⁵ Eteplirsen targets a subset of patients with DMD who are amenable to exon 51 skipping.

¹⁴⁶ Appeal at 16.

Some may argue that it would be reasonable to proceed with accelerated approval based on eteplirsen's safety profile, even where there are significant doubts about the drug's effectiveness. That argument does not take into account the risks of treatment with indwelling catheters to maintain vascular access in young patients, who would otherwise not need one and who often receive adjunct chronic corticosteroids, or, even more importantly, the detrimental impact on their quality of life.

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202¹⁴⁷—which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings. As determined by the review team, and as acknowledged by Dr. Woodcock, the article's scientific findings—with respect to the demonstrated effect of eteplirsen on both surrogate and clinical endpoints—do not withstand proper and objective analyses of the data. Sarepta's misleading communications led to unrealistic expectations and hope for DMD patients and their families. It is very disappointing that the findings did not hold up to careful review.

FDA must remain steadfast in its commitment to alleviating pain and suffering, approach the most challenging problems with absolute determination, and apply maximum flexibility to facilitate the development and availability of effective treatments. The agency's value centers on its ability to do all of the above while maintaining objectivity, even in the face of political pressure. FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard.

I acknowledge that there are currently no specific drugs available to treat patients with DMD and that issuance of a complete response letter would cast uncertainty on whether eteplirsen would continue to be developed, based on business and financial decisions that are external to FDA. However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions. Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.

I remain deep in my conviction that, through science and a flexible, sound regulatory approach, good therapies will emerge to provide meaningful clinical benefit to patients with DMD and other rare serious diseases.

THE SDR BOARD'S ADDITIONAL RECOMMENDATION

Although the SDR Board acknowledges that the scope of our review, as prescribed by the SDR-SMG, is limited to procedural questions, we nonetheless feel duty-bound to make one additional recommendation. As noted above, Dr. Unger seeks from the Office of the Commissioner a substantive, scientific review of Dr. Woodcock's decision to grant accelerated approval to

¹⁴⁷ See Mendell JR, et al. *Ann Neurol* 2013;74:637-47.

eteplirsen. The SDR-SMG presumes that an initiator such as Dr. Unger has received some substantive review of the scientific dispute at issue as part of a formal appeals process in the Center. Dr. Unger has never received any such formal review of his scientific arguments or the underlying evidence. To the extent he has ever received any substantive review of his scientific disagreement with Dr. Woodcock, Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor. Neither the SDR-SMG nor CDER's SDR-SOPs contemplate a scientific disagreement that arises between a Center Director and another manager in that same Center—partly because no one has ever anticipated the unique circumstance of this case. Especially given the SDR Board's concerns regarding the decision-making process at CDER, we think additional review within the Office of the Commissioner is appropriate.

The SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit. If you choose the latter, in light of the public and political pressure evident during the entire review process at CDER, as detailed in this recommendation, we believe that delegating this critical evaluation to a panel of experts would help ensure that the agency makes the most appropriate decision from the perspective of protecting patients and the public health, especially for DMD patients. Knowing as we do that you value cross-Center collaboration with respect to medical product development, we recommend that you include on the panel experts from other Centers devoted to the regulation of medical products. Doing so would not only help ensure diverse expertise on the panel but also provide insights on the effects that any proposed regulatory decision on eteplirsen might have on products regulated by those other Centers. We further recommend that you consider whether to include experts from other components within the Department of Health and Human Services and whether, consistent with applicable laws and the appropriate timeframe for a decision, you should also include outside experts on the panel.

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: RE: Update on Eteplirsen Accelerated Approval?
Date: Wednesday, August 24, 2016 8:22:59 AM

Yes, will do. sl

From: Woodcock, Janet
Sent: Wednesday, August 24, 2016 8:20 AM
To: Ligon, Sharnell (CDER)
Subject: FW: Update on Eteplirsen Accelerated Approval?

Can you set up a call? Sometime this week. Tx! jw

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Tuesday, August 23, 2016 5:48 PM
To: Woodcock, Janet
Subject: RE: Update on Eteplirsen Accelerated Approval?

Dear Dr. Woodcock

Further to our telephone conversation on Friday 12 August, I wanted to check in with you regarding the approval date for eteplirsen. I recall you expected it to be this week? Is that still the case?

We are preparing our press release (PR) in anticipation of approval this week and wanted to know if FDA are planning to also have a PR. If that is the case, we would like to coordinate with you in terms of timing.

I look forward to hearing from you.

Regards,
Shamim

Shamim Ruff
SVP Regulatory Affairs and Quality
p 617-274-4009 c (b) (6)
e sruff@sarepta.com



215 First Street, Cambridge, MA 02142

From: Woodcock, Janet [<mailto:Janet.Woodcock@fda.hhs.gov>]
Sent: Friday, August 12, 2016 2:57 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: Update on Eteplirsen Accelerated Approval?

What is a good phone number for you? jw

From: Shamim Ruff [<mailto:SRuff@Sarepta.com>]
Sent: Friday, August 12, 2016 9:43 AM
To: Woodcock, Janet
Subject: Re: Update on Eteplirsen Accelerated Approval?

Dear Dr. Woodcock

I am so sorry to hassle you but do you have any further updates on the eteplirsen review process?

Kind regards
Shamim

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From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: FW: Sarepta communication
Date: Wednesday, August 24, 2016 8:22:40 AM
Attachments: [2016-06-01 FDA InfoRequest.pdf](#)

Good Morning Dr. Woodcock,

Please see below email from Dr. Califf. Could he be referring to the first document I sent you yesterday which is attached?

Thanks

Sharnell

From: Califf, Robert
Sent: Wednesday, August 24, 2016 8:03 AM
To: Ligon, Sharnell (CDER)
Subject: Re: Sarepta communication

Sharnell,

This is a letter from Janet. She had referred to a previous letter that was signed by the review group as I understood it.

Thx

Rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sharnell Ligon <Sharnell.Ligon@fda.hhs.gov>
Date: Tuesday, August 23, 2016 at 2:33 PM
To: apple <rmc1@fda.hhs.gov>
Subject: Sarepta communication

Dear Dr. Califf,

Per your request, attached is the letter that was sent to Sarepta.

Kind Regards,

Sharnell

From: [Matthew Rael](#)
To: [Choy, Fannie \(Yuet\)](#)
Cc: [Shamim Ruff](#)
Subject: RE: FDA Information: re: NDA 206488 / eteplirsen
Date: Wednesday, June 01, 2016 11:20:43 AM

Hi Fannie,

I acknowledge receipt.

We'll get back to you as soon as possible.

Regards,

Matt

Matthew Rael, MS

Senior Manager, Regulatory Affairs

p 617.274.4029 c (b) (6) f 617.812.0509

e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Wednesday, June 01, 2016 10:54 AM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Matthew Rael <MRael@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: FDA Information: re: NDA 206488 / eteplirsen
Importance: High

Dear Shamim:

We refer to NDA 206488 for eteplirsen submitted on June 26, 2015.

As you know, we were unable to complete our review by the PDUFA date of May 26, but we are committed to completing our review process in a timely manner. A critical component of our ongoing review is whether there is substantial evidence that eteplirsen increases the production of dystrophin, as such a finding could potentially support an accelerated approval. As you know, the dystrophin biomarker data from Study 201/202 include only two pre/post biopsy samples from boys originally randomized to Study 201, and these samples, and all but one of the samples from external

control boys, were obtained from a different muscle group. On May 5, you responded to our request for information about completed biopsies from the ongoing Promovi trial. You reported that baseline biopsies have been obtained from 62 boys in the eteplirsen-treated arm and that 10 boys each have undergone a biopsy following 24 and 48 weeks of eteplirsen treatment. Analysis of the data for immunohistochemistry and Western blotting from these additional biopsies would substantially enhance our assessment of whether eteplirsen treatment leads to dystrophin production. You suggested that a protocol amendment would require 3-6 months, because of the time needed to amend the protocol, distribute it to the sites, and gain IRB approvals. We are eager to work with you to explore ways we can collaborate to expedite the timeline for making these data available for review and will do all we can to assist you in this effort. We would like to schedule a teleconference with you in the next day or two to explore the most efficient options to obtain these analyses.

Please confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY

06/03/2016

At the request of Dr. Billy Dunn, DNP Director

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: RE: Sarepta letter/email re: biopsy
Date: Tuesday, August 23, 2016 2:22:16 PM
Attachments: [NDA206488_etepilrsen_FINAL_GeneralAdviceLtr.pdf](#)

Thanks. I believe this is it. sl

From: Woodcock, Janet
Sent: Tuesday, August 23, 2016 2:17 PM
To: Ligon, Sharnell (CDER)
Subject: RE: Sarepta letter/email re: biopsy

No this is an earlier one. The later one says at the end that if they can demonstrate a meaningful increase in dystrophin, we will grant accelerated approval within 4 business days. jw

From: Ligon, Sharnell (CDER)
Sent: Tuesday, August 23, 2016 2:14 PM
To: Woodcock, Janet
Subject: FW: Sarepta letter/email re: biopsy

Hi Dr. Woodcock,

I believe this is the email you are referring to. If so, would you like me to send this to Dr. Califf or retrieve the "cleaned up/final version" from DARRTS?

Sharnell

From: Choy, Fannie (Yuet)
Sent: Tuesday, August 23, 2016 2:05 PM
To: Ligon, Sharnell (CDER)
Subject: RE: Sarepta letter/email re: biopsy

Hi,

Please see the attached email for the request, and let me know if that's not what you're referring to.

Thanks
Fannie

From: Ligon, Sharnell (CDER)
Sent: Tuesday, August 23, 2016 1:53 PM
To: Choy, Fannie (Yuet)
Subject: Sarepta letter/email re: biopsy
Importance: High

Hi Fannie,

Do you have the final letter that was sent to Sarepta where we requested them to provide us with their biopsy samples?

Thanks

Sharnell

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
**Director, Center for Drug Evaluation and Research (CDER),
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 ICH 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 α -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. 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 corrected 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, data from Dr. Unger) 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.

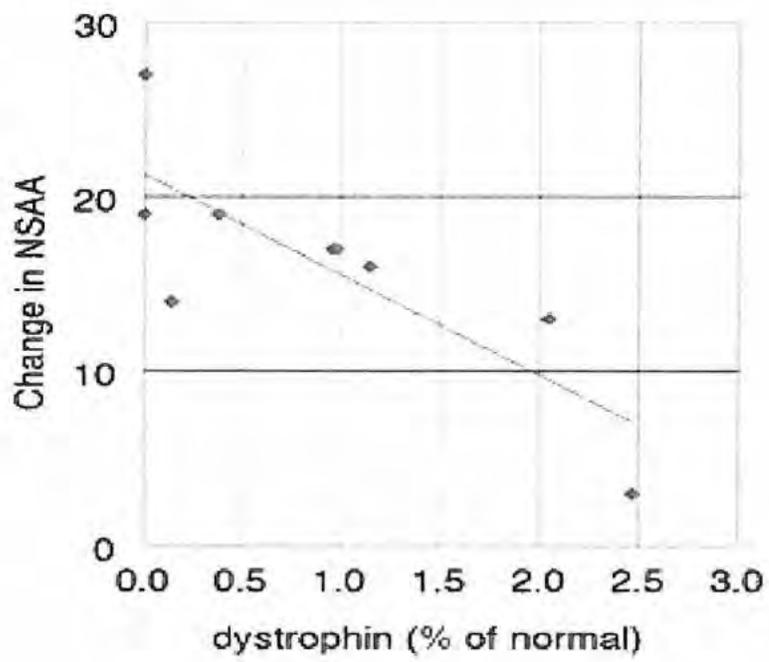
COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

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.

Figure 1



Appears this way on the original

From: [Rice, Crystal](#)
To: [Woodcock, Janet](#)
Cc: [Rice, Crystal](#)
Subject: RE: Draft CD note -- eteplirsen -- for your review
Date: Wednesday, August 03, 2016 11:46:12 AM

Hi Dr. Woodcock,

I received clarification: The data integrity study is scheduled to be sent to Dr. Califf by the end of the week. From there, Dr. Califf has up 30 days to make a decision. We are still a few weeks away from making a public announcement if they approve the product.

Thank you,
Crystal

From: Woodcock, Janet
Sent: Tuesday, August 02, 2016 4:06 PM
To: Rice, Crystal
Subject: RE: Draft CD note -- eteplirsen -- for your review

tx

From: Rice, Crystal
Sent: Tuesday, August 02, 2016 3:37 PM
To: Woodcock, Janet
Subject: RE: Draft CD note -- eteplirsen -- for your review

Oh! Okay, will do. I'll circle back.

From: Woodcock, Janet
Sent: Tuesday, August 02, 2016 3:32 PM
To: Rice, Crystal
Subject: RE: Draft CD note -- eteplirsen -- for your review

Yeah that would be good. I heard maybe this week. jw

From: Rice, Crystal
Sent: Tuesday, August 02, 2016 3:30 PM
To: Woodcock, Janet
Subject: RE: Draft CD note -- eteplirsen -- for your review

I heard it from Kim, but am not certain where she heard it from – would you like for me to check? I want to make sure we're on the same page in regard to timing.

Crystal

Crystal Rice
Internal Communications Program
Division of Health Communications
Office of Communications
U.S. FDA's Center for Drug Evaluation and Research
10001 New Hampshire Avenue, Rm 4178
Silver Spring, MD 20993
301-796-3111 Crystal.Rice@fda.hhs.gov

FDACDER0001131

From: Woodcock, Janet
Sent: Tuesday, August 02, 2016 3:29 PM
To: Rice, Crystal
Subject: RE: Draft CD note -- eteplirsen -- for your review

I hope it is not that far away. Who did you hear that from? I will have to work on this announcement. jw

From: Rice, Crystal
Sent: Tuesday, August 02, 2016 2:26 PM
To: Woodcock, Janet
Cc: Ligon, Sharnell (CDER); Rice, Crystal
Subject: Draft CD note -- eteplirsen -- for your review

Hi Dr. Woodcock,

Below/attached you'll find a draft of a Center Director note concerning eteplirsen. My understanding is that an anticipated action is still a few weeks out, but I was asked by OCOMM leadership to send you the draft for early review. The content is derived from a combination of the draft external materials and your decisional memo.

Please advise on any changes, at your convenience.

Thank you,
Crystal

Email subject line: **Approval of first drug for Duchenne muscular dystrophy**

CDER Staff:

Today, FDA approved the first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children. The drug, Exondys 51 (eteplirsen) injection, is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects approximately 13 percent of the population with DMD.

Exondys 51 was approved under the accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy. Accelerated approval is based on data that shows the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production at a low-level in some patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.

While accelerated approval provides earlier patient access to promising new drugs, under its provisions FDA requires the sponsor to conduct clinical trials to verify the predicted clinical benefit of the drug. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to show that the drug improves motor function.

The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework. In this case, 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. These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under

the accelerated approval pathway.

This approval is a good example of our dedication to approving treatments for rare diseases, and to the patient's voice brought to FDA.

In June 2015, FDA issued a [draft guidance](#) for industry on developing drugs for the treatment of DMD and related dystrophinopathies – one year following our receipt of a proposed draft guidance for consideration from the advocacy group, Parent Project Muscular Dystrophy (PPMD). This effort highlights how collaboration between engaged stakeholders and FDA can contribute to drug development. We appreciate PPMD's tireless efforts, and value their and the DMD community's input.

FDA first looked at this drug at the April 25, 2016 [advisory committee meeting](#). The advisory committee recommendations were two-fold. On accelerated approval, the committee recommended the applicant provide substantial evidence from studies that the drug induces production of dystrophin to a level that is reasonably likely to predict a clinical benefit. As it concerns traditional approval, the advisory committee recommended that there was not substantial evidence that the drug is effective in providing clinical benefit.

I would like to acknowledge the work done by the review team. The time spent to evaluate the application data and scientific discussions was much appreciated.

We will continue to work with sponsors to facilitate the development and approval of effective treatments for DMD and other rare diseases.

For more information about DMD, and today's approval, visit (*Press release URL pending*).

Janet Woodcock

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From: [Borio, Luciana](#)
To: [Woodcock, Janet](#)
Cc: [Warren, Matthew](#)
Subject: SDR-Board - eteplirsen - appeal
Date: Tuesday, August 09, 2016 11:39:30 AM

Dear Dr. Woodcock,

On behalf of FDA's Scientific Dispute Resolution Board, I'm writing to let you know that I have submitted to Dr. Califf the Board's findings and recommendations with respect to the appeal submitted by Dr. Unger, under Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA" (the SDR-SMG). As you know, Dr. Unger challenged the basis for your decisional memorandum concluding that a new drug application (NDA) submitted by Sarepta Therapeutics Inc. for eteplirsen, a drug intended to treat Duchenne muscular dystrophy (DMD), meets the standard for accelerated approval under 21 CFR § 314.510. This morning I had the opportunity to brief Dr. Califf on the Board's recommendations. Dr. Califf is reviewing the matter and is expected to make a decision, with regard to next steps, in the coming weeks.

Sincerely,

Lu

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/BLA #: 206488

Drug Name: EXONDYS 51™ (eteplirsen)

Indication(s): Duchenne muscular dystrophy (DMD)

Applicant: Sarepta

Date(s): Submission date: 6/26/2015
PDUFA Date: 2/26/2016

Review Priority: Priority Review

Biometrics Division: Division I, Office of Biometrics (HFD -710)

Statistical Reviewer: Xiang Ling, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader
Jim Hung, Ph.D., Director

Medical Division: Division of Neuropharm (HFD -120)

Clinical Team: Christopher Breder, M.D., Ph.D.
Ronald Farkas, M.D., Ph.D., Team Leader

Project Manager: Fannie Choy

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1 EXECUTIVE SUMMARY

The data, overall, did not provide statistical evidence to support the efficacy of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The only randomized controlled study submitted by the applicant, Study 201, can only be considered as exploratory because of study design and statistical analysis issues. In Study 201, patients were randomized to receive 50 or 30 mg/kg eteplirsen, or placebo. The study endpoints were assessed through Week 24. The statistical analysis plan of Study 201 did not include a method for statistical adjustment for testing multiple doses and/or multiple endpoints. The primary endpoint in Study 201 was the percent of dystrophin positive fibers in muscle biopsy tissue. The interpretation of the immunohistochemistry raw data is discussed in the clinical review. There was no nominally significant difference between eteplirsen 50 mg/kg, eteplirsen 30mg/kg and placebo for the 6MWT, which was the key clinical endpoint in Study 201.

The comparison of eteplirsen with historical controls, as proposed by the applicant in the open-label extension of Study 201 (called Study 202 by the applicant), is statistically uninterpretable, as this open-label extension did not have a prespecified statistical analysis plan, and had an inadequate control for bias. Among the potential sources of bias in the open-label extension of Study 201 are possible differences in various factors between eteplirsen-treated patients and the selected historical control cohort unaddressed by the applicant's attempt to match patients, the potential selection bias due to the *post-hoc* identification of the control cohort by the applicant, and other known sources of bias with the use of a historical control.

2 INTRODUCTION

2.1 Overview

Study 201 is the only randomized, double-blind, placebo-controlled study in this application. It was conducted at a single site in US in 12 subjects with genotypically confirmed DMD. Efficacy was assessed through the first 24 weeks of this study, while safety was assessed through Week 28. Upon completion of Study 201, all 12 patients were enrolled into an open-label extension study (Study 202) to continue receiving once-weekly treatment with eteplirsen. Study 202 was still ongoing at the time of NDA submission and interim study results were submitted for a cumulative 168 weeks of treatment, from Week 1 in Study 201 through the interim data cut at Week 140 in Study 202.

A historical control cohort was identified from 2 DMD patient registries for comparison to eteplirsen-treated patients in Study 201/202.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\NDA206488\0001\m5\53-clin-stud-rep\535-rep-eflic-safety-stud\dmd-51 and \\CDSESUB1\evsprod\NDA206488\0006\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The key clinical efficacy endpoint results were reproduced by this reviewer from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The first patient was enrolled in Study 201 on July 18, 2011 and the study was completed on February 29, 2012. Protocol 201 was amended 7 times, 3 of them were implemented after the study was initiated and the last version was dated January 07, 2012. In Amendment 6 (dated November 04, 2011), the protocol changed the endpoint of 6-Minute Walk Test (6MWT) from exploratory endpoint to a secondary endpoint. In Amendment 7 (dated January 07, 2012), the duration of the study was extended from 24 to 28 weeks. The efficacy analyses were only specified in the statistical analysis plan (SAP), dated February 20, 2012.

Study 201 was not designed as a clinical efficacy study and not powered for efficacy analysis. The primary endpoint was the percent of dystrophin positive fibers as measured in muscle biopsy tissue, i.e., a biomarker. The key clinical secondary endpoint, 6MWT, was specified midway through the trial and the analyses were not specified until the trial was close to completion.

Study Design

This is a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of once-weekly i.v. infusions of eteplirsen in subjects with genotypically confirmed DMD with an appropriate genetic lesion. Eligible subjects were randomized to receive 50 or 30 mg/kg eteplirsen or placebo, then placebo subjects were further randomized to 1 of 2 groups to create 4 treatment groups as shown in Table 1. Groups 1 and 2 received 50 or 30 mg/kg eteplirsen once a week for 28 weeks. Group 3a received placebo once a week for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks, and Group 3b received

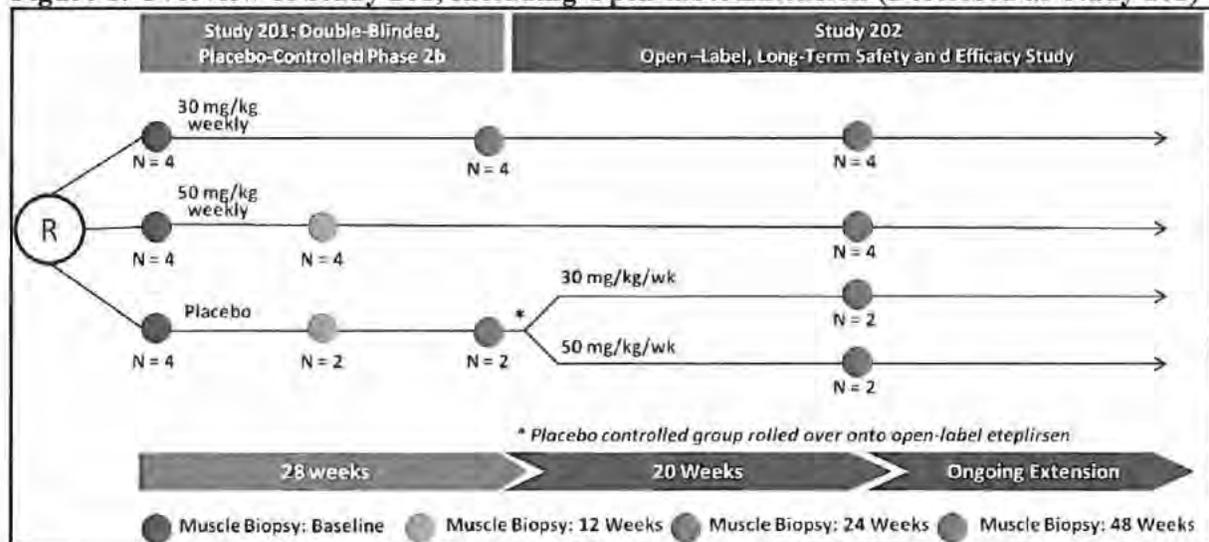
placebo once a week for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks. Beginning Week 25, all parties were aware that all subjects were receiving either 50 or 30 mg/kg eteplirsen.

Table 1: Treatment Groups

Group	N	Treatment
1	4	50 mg/kg eteplirsen IV once weekly for 28 weeks
2	4	30 mg/kg eteplirsen IV once weekly for 28 weeks
3a	2	Placebo IV for 24 weeks then 50 mg/kg eteplirsen for 4 weeks
3b	2	Placebo IV for 24 weeks then 30 mg/kg eteplirsen for 4 weeks

All patients underwent muscle biopsies at baseline for analysis of exon skipping and dystrophin expression. Repeat biopsies were performed at Week 12 for patients in Group 1 and Group 3a and at Week 24 for patients in Group 2 and Group 3b. Efficacy was assessed through the first 24 placebo-controlled weeks of this study, while safety was assessed through Week 28. Upon completion of this study, all 12 patients were rolled into an open-label extension (called Study 202 by the applicant) to continue receiving once-weekly treatment with eteplirsen for additional 212 weeks. In the open-label extension, all patients underwent a third muscle biopsy from the deltoid muscle at Week 20 and optionally a fourth muscle biopsy at approximately Week 140.

Figure 1. Overview of Study 201, Including Open-label Extension (Described as Study 202)



Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from baseline in percent of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry (IHC) at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.

Key Efficacy Endpoints:

1. Changes from Baseline in CD3, CD4, and CD8 lymphocyte counts in muscle biopsy tissue at Week 12 for groups 1 and 3a and at Week 24 for groups 2 and 3b.
2. Changes from Baseline to Week 24 in 6-Minute Walk Test (6MWT).

The following clinical assessments were described as exploratory endpoints in the protocol (Amendment 7, dated 07 January 2012), but are included as key secondary endpoints together with 6MWT in the SAP (dated February 20, 2012):

- Timed 4 Step Test.
- Maximum voluntary isometric contraction test (MVICT) to measure elbow flexion and extension, knee flexion and extension, and grip strength.
- Timed 10-meter run from the North Star Ambulatory Assessment (NSAA).
- NSAA total score.

There is no clear description of hierarchal ordering among all those secondary endpoints. In the open-label extension (described as Study 202) only 6MWT is included as primary clinical endpoint.

3.2.2 Statistical Methodologies

Testing and summary statistics of all efficacy endpoints will combine placebo subjects into a single group. Some efficacy assessments including 6MWT were performed on Days 1 and 2 of the Week 1 (baseline), Week 12, and Week 24 visits and once at the Week 4, 8, 16, and 20 visits. On those visits where 2 tests were performed, the maximum/best observed value is used for the primary analysis. If data for any one visit day are missing, then the non-missing value from the same visit is used.

Efficacy Analysis Population

The efficacy analysis set is the Full Analysis Set (FAS), consisting of all subjects randomized into the study who received any amount of study drug.

Statistical Analysis Method

For this exploratory study, all statistical analyses are conducted at two-sided alpha level of 0.05. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints, so all p-values are exploratory only.

The primary efficacy endpoint, the change from baseline in percent of dystrophin positive fibers, was analyzed by comparing the 50 mg/kg eteplirsen treatment group at Week 12 to the combined placebo treatment group, and the 30 mg/kg eteplirsen treatment group at Week 24 to the combined placebo treatment group, using the ANCOVA for ranked data with Baseline values and duration of DMD as covariates.

The analysis of changes from baseline to Week 24 in the clinical assessment parameters (6MWT, Timed 4 Step Test, MVICT, Timed 10-meter run, and NSAA total score) was based on a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) with treatment (placebo, 30 mg/kg, 50 mg/kg), time, and treatment-by-time interaction terms as fixed effects, subject nested within treatment as random effects, with the Baseline value and time since DMD diagnosis as covariates. A first-order autoregressive (AR1) covariance structured matrix is used. The treatment comparison is made between each of the active treatments and placebo. The same MMRM analysis described above would be repeated to compare the combined eteplirsen groups to placebo.

If there was strong evidence suggesting that data for any endpoint deviated from normal distribution, then ANCOVA for ranked data was to be utilized.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were recruited for this study nationwide across the US. A total of 12 patients were randomized and all patients received scheduled infusions of study medication and completed the study as planned. All patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white. The time since DMD diagnosis ranged from 18 to 112 months, with a median duration of 57 months. Numerically, there appears to be some imbalance in baseline 6MWT among the treatment groups (Table 2).

Table 2: Demographic and Baseline Disease Characteristics

Parameter		Placebo to	Eteplirsena			All Patients
		Eteplirsena	30 mg/kg	50 mg/kg	All Eteplirsena	
		N = 4	N = 4	N = 4	N = 8	N = 12
Age	Mean	8.5	9.3	8.5	8.9	8.8
	Median	8.5	9	8.5	9	9
	Min, Max	7, 10	9, 10	7, 10	7, 10	7, 10
Mutation, n (%)	45-50	0	2 (50.0)	1 (25.0)	3 (37.5)	3 (25.0)
	48-50	0	1 (25.0)	0	1 (12.5)	1 (8.3)
	49-50	3 (75.0)	0	2 (50.0)	2 (25.0)	5 (41.7)
	50	1 (25.0)	0	0	0	1 (8.3)
	52	0	1 (25.0)	1 (25.0)	2 (25.0)	2 (16.7)
6MWT, meters	Mean	394.5	355.3	396	375.6	381.9
	Median	379	359	395	380.5	380
	SD	42.25	74.78	26.61	56.34	50.92
	Min, Max	364, 456	261, 442	365, 429	261, 442	261, 456
Time since DMD diagnosis, months	Mean	50.3	52.5	66.5	59.5	56.4
	Median	51	57	68	57	57
	SD	13.74	14.06	44.29	31.33	26.4
	Min, Max	36, 63	32, 64	18, 112	18, 112	18, 112

^a Includes both 30 mg/kg and 50 mg/kg

Source: Table 10-2 and 10-3 of the CSR.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

The following analyses were based the fiber data derived by the applicant. The validity of the immunohistochemistry (IHC) raw data is beyond the scope of this review, and is addressed in the clinical review, to which the reader is referred for interpretation of the IHC results.

There was no statistically significant difference between the 50 mg/kg eteplirsena group and placebo at Week 12 ($p=0.958$; Table 3). At Week 24, the mean percentage of dystrophin-positive muscle fibers was higher in the eteplirsena 30 mg/kg group than the placebo. Patients treated with 30 mg/kg eteplirsena demonstrated 23% increase in the mean percentage of dystrophin positive fibers from baseline to Week 24. There appeared to be no increases from baseline in placebo patients. The nominal p value (0.002) for the comparison between eteplirsena 30 mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type 1 error due to multiple comparisons, and the other comparison between 50mg/kg and placebo in Study 201 was negative.

Table 3: Dystrophin-Positive Fibers Detected by IHC with MANDYS106

Time point		Placebo	30 mg/kg Eteplirsen N = 4	50 mg/kg Eteplirsen N = 4
Baseline	Mean	15.64	18.19	11.00
	Median	15.58	17.80	11.51
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment	Mean	11.59	41.14	11.79
	Median	9.44	38.77	11.81
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95	0.79
	Median	-6.13	23.46	2.52
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4
	p-value ^a		0.002	0.958

Source: CSR Table 11-1 and Table 14.2.1.1.2, confirmed by FDA reviewer.

^aBased on ANCOVA model for ranked data with treatment (placebo, 30 mg/kg, 50 mg/kg) as a fixed effect and baseline value and time since DMD diagnosis as covariates.

3.2.4.2 Analyses of 6MWT

As shown in Table 4, placebo-treated patients experienced a mean decline of 17.3 meters in 6MWT from baseline to Week 24, while patients in the 30 and 50 mg/kg eteplirsen groups showed mean declines of 134.8 and 2.3 meters, respectively. ANCOVA for ranked data showed no nominally significant differences between the treatment groups. The result of the MMRM analysis showed a nominally statistically significant difference between the placebo and 30 mg/kg eteplirsen groups, in favor of placebo (p=0.026; Table 4).

Table 4: Analysis Results of Change from Baseline in 6MWT

	Placebo	30mg/kg Eteplirsen N = 4	30mg/kg Eteplirsen mITT N = 2	50mg/kg Eteplirsen N = 4
Baseline				
Mean	394.5	355.3	407	396
Median	379	359	407	395
SD(SE)	42.25(21.12)	74.78(37.39)	49.50(35.00)	26.61(13.30)
Min, Max	364, 456	261, 442	372, 442	365, 429
Week 24				
Mean	377.3	220.5	394.5	393.8
Median	377.5	204	394.5	403.5
SD (SE)	19.00 (9.50)	203.14 (101.57)	51.62 (36.50)	53.67 (26.84)
Min, Max	354, 400	43, 431	358, 431	325, 443
Change at Week 24				
Mean	-17.3	-134.8	-12.5	-2.3
Median	-12	-116	-12.5	1.5
SD (SE)	28.06 (14.03)	144.71 (72.36)	2.12 (1.50)	29.89 (14.95)
Min, Max	-56, 11	-296, -11	-14, -11	-40, 28
treatment effect*		-102.4		25.6
95% CI *		(-192.2, -12.5)		(-62.7, 113.8)
P-value *		0.026		0.563

*Based on mixed model repeated measures (MMRM).

Source: Table 14.2.5.2.1 and Table 14.2.5.2.2 of Study 201 CSR,

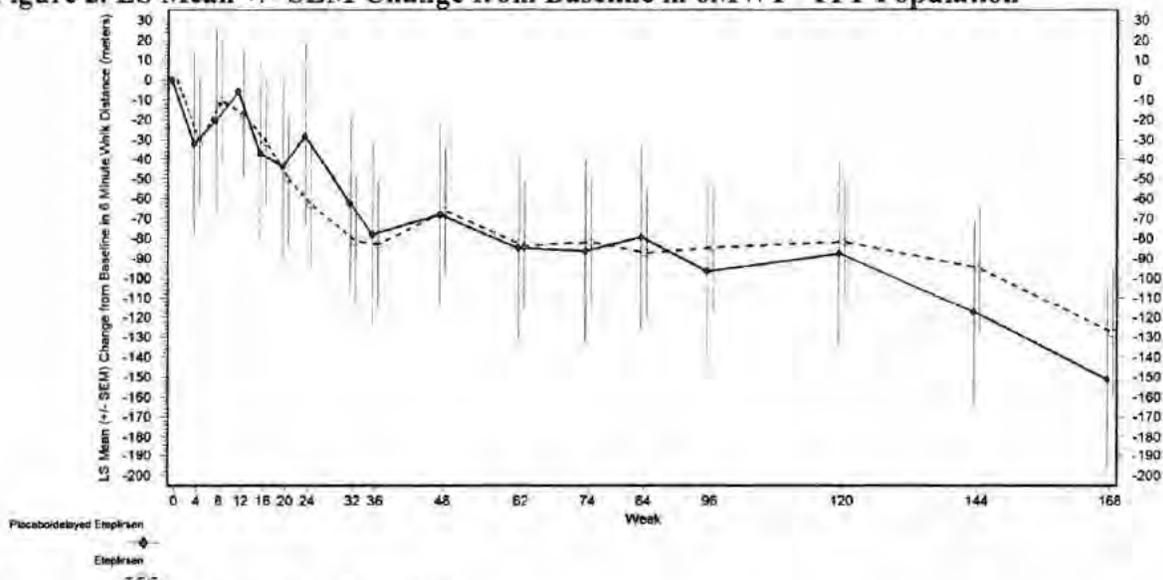
The applicant stated that the large decline in the 30 mg/kg eteplirsen group was attributable to Patients 009 and 010, who showed signs of rapid disease progression within weeks after enrollment. Therefore, the applicant conducted *post-hoc* analyses using Modified Intent-to-Treat (mITT) Population which excluded those 2 patients. For the mITT population, the mean change from baseline to Week 24 in MWT was a decline of 12.5 meters for the 30 mg/kg eteplirsen group. Both ANCOVA on ranked data and the MMRM analysis showed no nominally significant differences between the treatment groups in mITT.

The mITT population was not pre-specified in the SAP. Moreover, the mITT was defined based on the outcome data (instead of enrollment criteria or baseline character). Therefore, analysis on the mITT population could be misleading.

3.2.4.3 Analyses of the open-label extension study (described by the applicant as Study 202)

The 6MWT at Week 168 was compared between the combined eteplirsen group and placebo/delayed eteplirsen group. Analyses on ITT population did not achieve nominal statistical significance ($p=0.68$ by MMRM). The changes from baseline in 6MWT by assessment week for the combined eteplirsen group and placebo/delayed eteplirsen group are shown in Figure 2.

Figure 2. LS Mean +/- SEM Change from Baseline in 6MWT - ITT Population



Source: Figure 14.2.5.2.2.1 of Study 202 CSR.

3.2.4.4 Comparison against Historical Controls

Historical Control Cohort

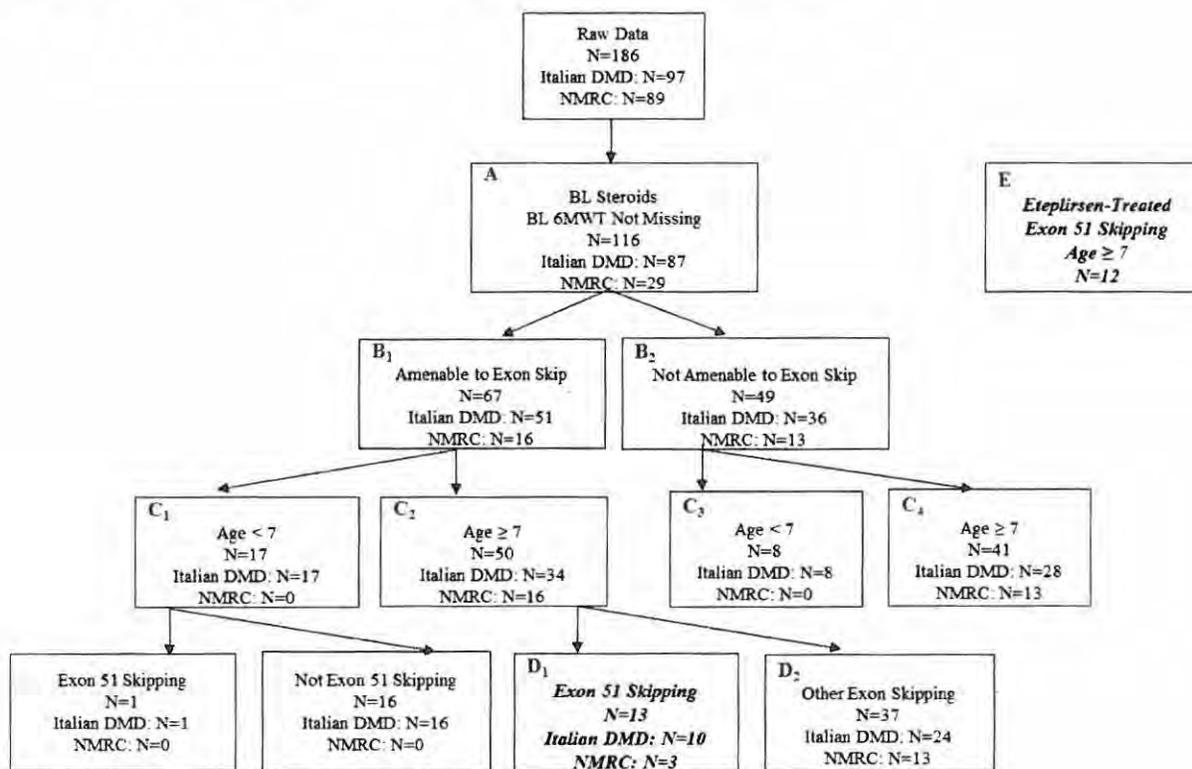
The comparison of eteplirsen with historical controls was not part of an adequate and well-controlled study. The applicant obtained historical data after observations were made for the eteplirsen patients. Historical data were obtained from 2 DMD patient registries (Italian DMD Registry and the Leuven Neuromuscular Reference Center – NMRC) for comparison to eteplirsen-treated patients. The following filters were applied to try to match patients in the historical control cohort:

1. Corticosteroid use at Baseline (use/non-use)
2. Sufficient longitudinal data for 6MWT available
3. Age ≥ 7 years
4. Genotype amenable to any exon skipping therapy
5. Genotype amenable to exon 51 skipping therapy

The Italian DMD registry is a longitudinal multicenter observational cohort study involving 11 tertiary neuromuscular centers in Italy. Patients were recruited between January 2008 and June 2010 and were to be followed for at least three years. The Italian DMD cohort contained the 6MWT results at Baseline (Month 0) and at Months 12, 24, and 36, with age and steroid use entered for each visit and with genotype information for 97 patients. Of these patients, 10 valid cases were identified based on applying the 5 filters.

The NMRC registry was an observational, single center, cohort study of DMD up to 17.5 years of age attending the NMRC between January 2007 and September 2012. The NMRC dataset contained 6MWT results at various time points, the patient's age and steroid use at the same time points, and genotype information for 89 patients. However, discrete visit designations (i.e., Baseline, Month 12, etc.) were not identified in the dataset. The first time points with non-zero meters on the 6MWT assessment for patients who were ≥ 7 years of age and on a steroid, were designated as the Baseline visit. Only 3 cases were identified based on applying filters (Figure 3).

Figure 3: Historical Controls and Eteplirsen-Treated Cohort



Source: Figure 1 of Study SR-15-031 CS.

Applicant's Comparison of Eteplirsen with Historical Control

The results for 6MWT in eteplirsen-treated patients compared with historical controls matched on all 5 criteria mentioned above are shown in Table 5. The difference in LS mean change from baseline on 6MWT at 36 months was 141 meters. The nominal p-value reported by the applicant is not meaningful because the open label extension with historical control comparison was not an adequate and well-controlled study, for the reasons described below.

Table 5: Applicant's Result of 6MWT in Eteplirsen Compared to Historical Controls

Patients Included	Groups Compared		Age	6MWT Baseline	6MWT Month 36**
HC + eteplirsen-treated, Steroid-Treated, Amenable to Exon 51 Skipping, ≥7 years old	HC	N	13	13	11
		Mean / LS Mean ^a (SE)	9.45 (0.403)	357.6 (18.51)	115.1 (33.54)
		Min, Max	7.3, 11.8	200, 458	
	eteplirsen-treated	N	12	12	12
		Mean / LS Mean ^a (SE)	9.41 (0.342)	363.2 (12.18)	256.4 (33.11)
		Min, Max	7.3, 11.0	256, 416	

* LS Mean for 6MWT Month 36 only

** LS Mean difference =141 and p=0.009 at month 36.

Source: Applicant's analyses with output table modified by the reviewer.

Reviewer's Discussion and Conclusion of the Historical Control Study

According to the ICH E10 guidance on Control Group and Related Issues in Clinical Trials, the major and well-recognized limitation of externally controlled (including historical control) trials is inability to control bias. The test group and control group can be dissimilar with respect to a wide range of observable and unobservable factors that could affect outcome. It may be possible to match the historical control group to the test group in observed factors but there is no assurance for any unobserved factors. "The lack of randomization and blinding, and the resultant problems with lack of assurance of comparability of test group and control group, make the possibility of substantial bias inherent in this design and impossible to quantitate."

Because of the serious concern about the inability to control bias, the use of the external control design is restricted only to unusual circumstances.

1. ICH E10 states that "an externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable..." However, such prior belief does not exist for eteplirsen.
2. ICH E10 states that "use of external controls should be limited to cases in which the endpoints are objective..." However, performance on the 6-minute walk test can be

influenced by motivation. Patients may not achieve maximal 6MWT due to concerns of falling or injury, or patients could try harder with encouragement and with the expectation that the drug might be effective.

3. Pocock's criteria¹ for acceptability of a historical control group require that "the methods of treatment evaluation must be the same," and "the previous study must have been performed in the same organization with largely the same clinical investigators." This is especially important when assessing endpoints such as 6MWT, in contrast to hard endpoints such as mortality. For this NDA, these requirements are not met.

Moreover, the historical control group was identified *post-hoc* in this NDA, leading to potential selection bias that cannot be quantitated. If a historical control is to be utilized, selection of the control group and matching on selection criteria should be prospectively planned without knowing the outcome of the drug group and control group.

Based on ICH E10, "a consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." The success criteria for this historical control study were not discussed or pre-specified in the protocol.

Given all these concerns, including issues of comparability of eteplirsen-treated patients and historical control cohort patients, the fact that 6MWT is not a "hard" efficacy endpoint, the potential of selection bias due to the *post-hoc* identification of the control cohort by the applicant, and all the known pitfalls with the use of historical controls, the comparison of the eteplirsen with the historical control is not statistically interpretable.

3.3 Evaluation of Safety

Please see the clinical review.

¹ Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases*. 1976; 29:175–188.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses are not applicable as the study 201 was conducted at a single site in the US and all 12 patients were 7 to 10-year old male and, except for one patient of Asian descent, all were white.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 201 was designed as an exploratory study. No multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints.

The sample sizes of both Study 201 and the historical control study are very small. The robustness of the study result is a concern since a single patient can change the results substantially. The interpretation of results is also difficult because the sample may not represent the DMD patient population at large. Small studies can be useful for hypothesis generating but usually do not have the ability to provide definitive evidence for a drug's effect.

5.2 Collective Evidence

In Study 201, there was no statistically significant difference between the 50 mg/kg eteplirsén group and placebo at Week 12 ($p=0.958$). Treatment with 30 mg/kg eteplirsén for 24 weeks increased the mean percentage of dystrophin-positive muscle fibers in DMD patients compared to placebo, however, the nominal p value (0.002) can only be considered exploratory due to the lack of multiplicity control.

The MMRM analysis of 6MWT at Week 24 in Study 201 showed a statistically significant difference between the placebo and 30 mg/kg eteplirsén groups, in favor of placebo ($p=0.026$). There was no statistically significant difference between the 50 mg/kg eteplirsén group and the placebo ($p=0.563$). These results must be considered as exploratory only.

The open-label extension with historical control is not statistically interpretable.

5.3 Conclusions and Recommendations

The data overall did not provide statistical evidence to support the efficacy in subjects who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

From: [Warren, Matthew](#)
To: [Woodcock, Janet](#)
Cc: [Behr, Virginia L](#)
Subject: Scientific Dispute Resolution Appeal
Date: Friday, July 29, 2016 3:57:42 PM
Attachments: [SDR SMG.pdf](#)
[Eteplirsen Appeal Unger 7-18-16.pdf](#)

Dr. Woodcock,

As you are probably already aware, I am helping coordinate review of an appeal related to your decisional memo regarding the NDA for eteplirsen. On July 18, we received an appeal of your decisional memo from Dr. Ellis Unger. Although Virginia Behr tells me that she has already forwarded you a copy of the appeal, I have attached another one for your convenience.

Under Staff Manual Guide (SMG) 9010.1 (also attached), employees from the Centers may elevate scientific disputes to the Office of the Commissioner by submitting an appeal. The first step of the process for the appeal is a procedural review by a standing committee ("the SDR Board"), which is chaired by the Acting Chief Scientist and made up of representatives from the Office of the Chief Scientist and Ombudsmen from around the agency. The SDR Board conducts a review of the processes used by the Center, including whether the appellant had a fair opportunity to present his views and whether the Center considered all relevant evidence.

The reason I am reaching out now is to see if you would be interested in meeting with the SDR Board to present your views of the decision-making process at CDER during the review of the NDA for eteplirsen. Our focus would be on the two key questions at issue, i.e., whether Dr. Unger had a fair opportunity to present his views and whether all relevant evidence was considered. Although the SMG encourages Center Directors to cooperate with the SDR Board in its inquiry, I leave it to your discretion as to whether you think it would be worthwhile to meet with the SDR Board for this appeal. Truth be told, the SDR Board would be very interested in hearing your perspective on the scientific dispute and its resolution within CDER. If possible, we would be interested in meeting with you the early part of next week.

Hope you have a nice weekend.

Regards,
Matt

G. Matthew Warren
Director
Office of Scientific Integrity

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Agency Scientific Dispute – Appeal

Date: July 18, 2016

To: **G. Matthew Warren**
Director
Office of Scientific Integrity, FDA

From: **Ellis F. Unger, M.D. (initiator)**
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Re: **NDA #** 206488
Drug: eteplirsen (Exondys 51)
Applicant: Sarepta Therapeutics
Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

1. Background

The Office of New Drugs within the Center for Drug Evaluation and Research (CDER) oversees regulation of new drugs, and is responsible for making regulatory decisions for approval/non-approval of new molecular entities. Within the Office of New Drugs, there are 6 sub-offices, including the Office of Drug Evaluation-I. The Office of Drug Evaluation-I oversees the Division of Neurology Products, which regulates drugs for the central and peripheral nervous systems, as well as drugs for muscular disorders. Typically, a new drug application (NDA) for a new molecular entity for a neurology indication is reviewed by the Division of Neurology Products in concert with review staff from other offices in CDER.¹ The regulatory decision is typically rendered by Office of Drug Evaluation-I, i.e., the signatory authority.

NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a *complete response* action. This view was shared by the Office of Biometrics, which performed the statistical review, as well as the Office of Clinical Pharmacology, which performed the pharmacology review. Dr. John Jenkins, Director, Office of New Drugs, also supports a *complete response* action for this NDA (verbal communication).

This memo is meant to explain the salient arguments around the scientific disagreement here; additional details are available in my memo recommending a complete response and Dr. Woodcock's memo recommending approval, and the reader is referred to those memoranda.

Disease Background:

¹ Reviews are typically provided by Office of New Drug Quality Assessment, Division of Medication Error Prevention and Analysis, Office of Biometrics, Office of Scientific Investigations, and others.

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys.

Dystrophin protein is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation. Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, there is loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Steroids are currently the cornerstone of management, widely believed to delay loss of ambulation and respiratory decline by several years.

Drug Background:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, by restoring of the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.

Drug Development Background:

Three studies are germane to the issues here. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study (see below).

The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.

2. Description of How My Position Differs from the Center's Perspective

Dr. Janet Woodcock, Director, CDER, disagrees with some of the findings of the review team, and has reached the conclusion that the NDA should be approved. She finds that the data meet the standard for accelerated approval under 21 CFR 314. 510, based on the change in a surrogate endpoint of dystrophin protein production – a change she concludes is reasonably likely to predict clinical benefit. The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit. The decision of *approval vs. complete response* hinges on this question.

a. Clinical/Statistical Efficacy

Accelerated Approval:

Dr. Woodcock has reached the conclusion that eteplirsen should receive accelerated approval based on a small effect on the surrogate endpoint of dystrophin production.

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept "...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied. There is no disagreement.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 2) whether the effect demonstrated meets the test of being "reasonably likely" to predict clinical benefit. Importantly, there is no regulatory definition of "reasonably likely."

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. There is no disagreement here.

The second part of factor 3 is whether an effect has been demonstrated; the legal standard is ‘substantial evidence’ based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05, but in some situations FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness.² Dr. Woodcock believes that “...there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.” I agree that there is evidence from a single adequate and well controlled trial, Study 301, that eteplirsen induces dystrophin production in muscle cells, but do not agree that there is reliable quantitative evidence from the other trial, Study 201/202.

The third part of factor 3, the conclusion that the demonstrated effect is “reasonably likely” to predict clinical benefit, is where there is disagreement.

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

Dr. Woodcock cites 3 lines of evidence pertinent to the conclusion that eteplirsen increases dystrophin production:

1. Production of an appropriate mRNA transcript
2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot
3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

1. Production of an appropriate mRNA transcript

I agree that the applicant has shown expression of mRNA following treatment with eteplirsen. As noted by Dr. Woodcock, this finding establishes proof of concept, but does not by itself mean that there is increased dystrophin production.

2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot

Western blot is a standard laboratory technique used to quantify proteins in body tissues. In Sarepta’s development program, Western blot was used to assess dystrophin protein levels in skeletal muscle in Study 201, in Study 202 (again, these were Study 201 patients who were maintained on treatment), and finally in Study 301.

a. Study 201:

The original Western blot analyses from Study 201 were intended to show that dystrophin levels were greater in eteplirsen-treated patients than in patients in the placebo group, and analyses were planned to compare the effects of the lower vs. higher eteplirsen doses on dystrophin production. The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.

b. Study 202:

² See: “Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;” May, 1998.

With FDA's assistance, the applicant improved the assays and performed repeat biopsies on 11 of 12 patients of the Study 201/202 patients at Week 180. These were to be compared to stored baseline (pre-treatment) samples; however, evaluable tissue was available for only 3 of the 11 patients. The baseline samples are germane to the determination of the treatment effect because the Week 180 biopsies showed only a small quantity of dystrophin (mean = 0.93% of normal). Thus, for the purpose of computing the *change* in dystrophin resulting from eteplirsen treatment, even small differences in the baseline level are critical.

As noted by Dr. Woodcock, the review team and I had concerns about these controls, leading us to conclude that Study 201/202 was not adequate and well controlled:

1. The goal was to assess the change in dystrophin with treatment, i.e., pre-treatment vs. post-treatment, but most of the baseline biopsies were obtained from subjects external to Study 201/202, who could differ in unknown ways from subjects in Study 201/202.
2. For all patients, the Week 180 biopsies were obtained from different muscles than the baseline biopsies, and studies of both normal human muscle and non-clinical DMD models have shown that dystrophin levels vary among muscles.
3. The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline, accordingly.

Dr. Woodcock believes that "...these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion." She notes that the external control patients were similar in age and mutation site to the patients in Study 201/202. She found little difference between dystrophin results across different muscle groups, and little difference based on storage time, leading her to believe that these factors "...did not result in large differences in the findings."

Although I agree that these factors are not likely to lead to large differences, even small differences would affect the calculation of the *change* in dystrophin at Week 180, because the Week 180 values were quite small (mean only 0.93% of normal). At issue is how much of the dystrophin detected at Week 180 was newly produced, vs present at baseline. For example, a difference in the baseline level of only 0.30%, although minute, is substantial compared to 0.93%.

Dr. Woodcock notes that at Week 180, 2 subjects had dystrophin levels between 2 and 3%, 2 had a level between 1 and 2%, and 2 had a level of ~1%. She notes that 2 of these subjects had both baseline and Week 180 samples, and there were clear increases in dystrophin in these 2 patients. Of note, Dr. Woodcock points out that although some subjects had Week 180 dystrophin levels similar to the baseline (i.e., close to zero), she would expect this because she would not predict that all individuals would respond to a drug intervention.

She explains that 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.”

In the end, taking Dr. Woodcock’s arguments into consideration, my view is that the data from Study 202 are *suggestive* of an increase in dystrophin in response to eteplirsen, but the study was not adequate and well controlled. If we accept that there *is* a difference, Study 202 does not reliably speak to the *amount* of dystrophin produced by eteplirsen, given the concerns above. There is only certainty that the largest *possible* amount was 0.93% of normal (on average), and <3% in any individual (if we assume that the quantity was zero at baseline).

Below I will present another concern that leads me to question the veracity of the Western blot data from the Week 180 biopsies from Study 202, based on an issue that Dr. Woodcock did not address in her memo.

c) Study 301:

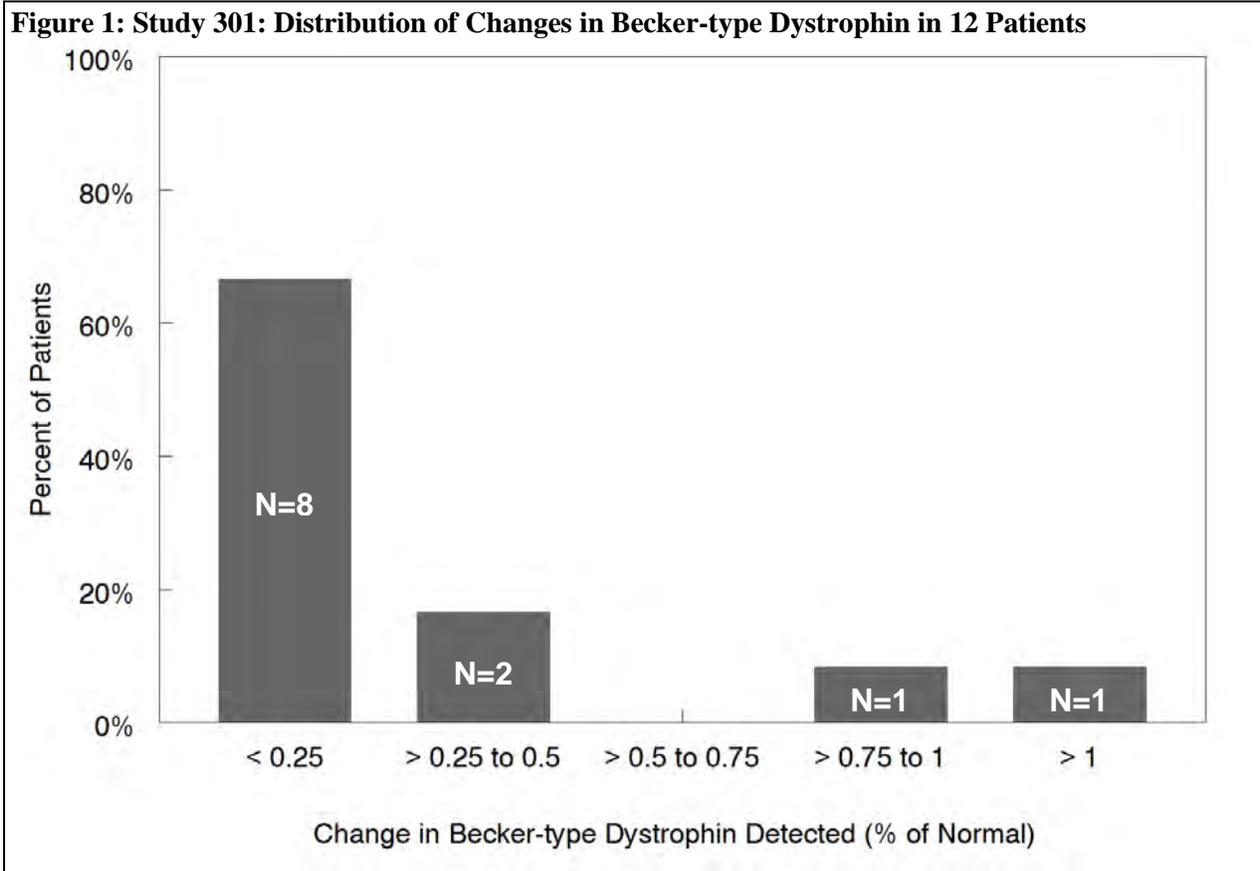
With the May 26, 2016 goal date approaching, OND and CDER could not reach agreement on the regulatory action for this NDA. In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301, PROMOVI). These samples were originally planned to be analyzed at the end of the study; however, we requested an interim analyses of a subset of samples. Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples obtained at baseline (prior to treatment) were compared to those obtained at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

The data are shown in Table 1 and the distribution of these changes is shown graphically in Figure 1. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change greater than 1%. The applicant used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.24	1.33
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08		
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	1.57	0.01
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17		
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12		
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31		
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09		
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34		
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25	13	Baseline	fail	0.34	0.18	0.03
		pass	0.17					pass	0.21		
	Week 48	fail	0.22	0.42			Week 48	fail	0.34		
		pass	0.42					pass	0.21		

All parties agree that these data were obtained from an adequate and well controlled study, and that there is a statistically significant effect of eteplirsen. The disagreement is whether or not the dystrophin production is at a meaningful level that is reasonably likely to predict clinical benefit.

To the extent that one can compare results across studies, these changes in dystrophin are even lower than the values obtained from Study 201/202 (the latter represent the quantity detected at Week 180, not the treatment effect). Dr. Woodcock wrote that “Only 2 of 12 patients achieved a level over 1% of normal control.” Her characterization refers to the amount of protein *detected* at Week 48, not the *change* in protein. In fact, only a single patient out of 12 had a *treatment effect* that exceeded 1%.



3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

Study 201/202 – Data through Week 48

Dystrophin production was assessed in Study 201 using immunohistochemistry, a standard laboratory procedure used primarily to localize proteins in tissue sections, but also used as a semi-quantitative method to measure dystrophin levels. Muscle samples were analyzed at baseline, and at Weeks 12, 24, and 48.

Dr. Woodcock notes “A finding of increased dystrophin was also seen in several IHC assays performed by the applicant.” She explains that several baseline and other pre-Week 180 assays were performed (from Study 201/202), but the validity of the results was questioned at the FDA inspection because of methodological issues, and so she does not consider these data further.

I do not agree with Dr. Woodcock’s outright rejection of these data. In fact, FDA requested a re-reading of the stored images by 3 masked pathologists under improved viewing conditions. We did not request any changes in immunohistochemistry methods or techniques, other than a different approach for selecting microscopic fields for image capture and analysis. Thus, we stressed that their stored images could provide useful data if properly read. The re-read

showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group. (The p -value is nominal because the type-I error rate was not controlled for multiplicity.) Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.

Study 201/202 – Week 180 Data

The applicant performed immunostaining along with Western blot analyses from the skeletal muscle biopsies obtained at Week 180.

Importantly, prior to performing these analyses, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Dr. Woodcock details the technical factors in her memo. Their aim was to determine the treatment effect for each patient, by comparing dystrophin levels at baseline and Week 180. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these samples with muscle tissue from 6 untreated external DMD patients, together to be compared to the Week 180 levels. Images were read by the same 3 pathologists, masked to treatment group.

Because external controls were used, the comparison of pre- vs. post-treatment values suffers from the same problems described for the Western blot analyses (i.e., different patients, different muscles, and possible loss of immunoreactive dystrophin with long-term storage).

These concerns notwithstanding, the applicant claimed a remarkable increase in dystrophin immunostaining at Week 180: the 9 baseline samples (from 3 patients in Study 201/202 and 6 external controls) showed $1.1\% \pm 1.3\%$ positive fibers (mean \pm SD), whereas the Week 180 samples (from 11 patients in Study 201/202) showed $17.4\% \pm 10.0\%$ positive fibers. I will note that FDA made no attempt to inspect or oversee these analyses.

Given that the original analysis showed, at baseline, 13% positive fibers for patients in Study 201/202, it is important to understand why the results from a new immunostaining protocol provided results of 1.1%, an order of magnitude lower.

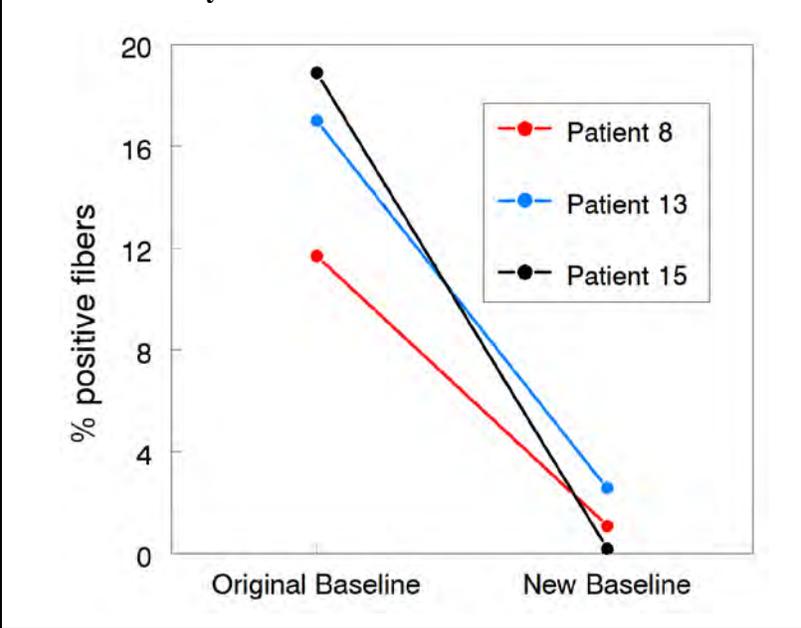
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue from baseline, which permitted a new immunohistochemistry analysis and a comparison of results between the old and new methods. Figure 2 shows how the two methods compare.

These are essentially replicate analyses of a single tissue sample using the two immunohistochemistry methods. There is an inexplicable difference of more than an order of magnitude between results of the old and new immunohistochemistry protocols. Such marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

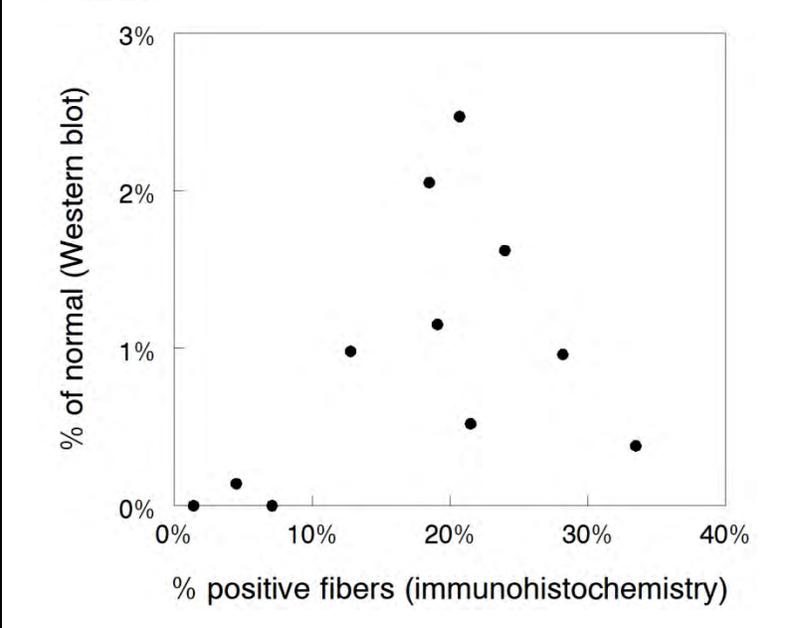
The integrity of the applicant's data is further called into question by lack of agreement between the immunohistochemistry and Western blot methods, i.e., a lack of internal consistency. The applicant claims to have enhanced both the immunohistochemistry methods and the Western blot methods in preparation for processing the Week 180 biopsies. Following these methodological improvements, single tissue blocks were subjected to both analyses – analyses considered to be complementary. Yet the lack of concordance between these two assessments of dystrophin levels is striking (Figure 3).

Figure 2: Comparison of Results from the New and Old Immunohistochemistry Protocols – Lack of Agreement for 3 Patients in Study 201/202



It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, the Western blot methods are inaccurate, or both methods are inaccurate. In light of the discordance between methods, the issues with the control samples, and the order-of-magnitude discrepancy between the old and new immunohistochemistry protocols, these data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Figure 3: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



A critical point is that results of immunohistochemistry analyses are method-dependent, and results from different laboratories are not directly comparable. Here we see a striking difference between results of different methods within a single laboratory.

Dr. Woodcock concluded “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).”

Although this statement does not constitute an important part of her argument in favor of dystrophin production, I do not agree that the immunohistochemistry data show an increase in dystrophin as a result of drug exposure. Given that changes in the immunohistochemistry protocol led to remarkably disparate results, and in light of the lack of correlation between dystrophin results as determined by immunohistochemistry and Western blot, I question the accuracy and interpretability of the Week 180 immunohistochemistry data. Moreover, the results from the properly blinded re-reading of the original data through the first 48 weeks of Study 201/202 are negative. I do agree, however, that the immunohistochemistry images appear to show dystrophin in the proper location, which helps support proof-of-concept.

In summary, I agree that there are data on dystrophin production from one adequate and well controlled study, Study 301, by Western blot. The amount of dystrophin produced and the likelihood of a clinical effect are discussed below.

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

As noted by Dr. Woodcock, “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.”

Without restating the details of Dr. Woodcock’s discussion, I generally agree with her basic summary of the many challenges of interpretation (quoted below). Most of her discussion speaks to the *uncertainties* inherent in correlating dystrophin levels with disease severity. I strongly agree that we lack a sound basis upon which to relate dystrophin levels observed in this development program to observations in the literature.

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

I agree. And importantly, as Dr. Woodcock notes, “the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized.”

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

I will add that the applicant’s own data show a striking difference between results of two somewhat different immunohistochemistry protocols conducted at the same laboratory (Figure 2). Thus, it would be treacherous to try to relate various levels of dystrophin, determined by immunohistochemical methods at various laboratories, to a particular clinical course.

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

Agree. Thus, is not feasible to relate levels of dystrophin determined by older Western blot methods, which lacked, for example, appropriate internal controls, to levels of dystrophin reported in these eteplirsen studies.

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

Agree. It is difficult to predict a protein’s function from its structure; even small changes in dystrophin structure can be important.

“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.”

Agree. There is little consensus on the relationship between dystrophin expression and clinical course at the low levels observed in eteplirsen-treated patients.

I also agree with Dr. Woodcock on the following points, and I paraphrase here:

- Dystrophin levels >10% on Western blot are usually associated with a BMD phenotype. Within the BMD phenotype, the relation between disease severity and protein expression is not clear. Protein quality, rather than quantity, may play a key role in determining phenotype in BMD.
- Patients with DMD are usually found to have undetectable levels of dystrophin, or very low levels. Dr. Woodcock notes that she believes the conventional threshold of <10% protein resulting in DMD was based on immunohistochemistry data. She tries to make a conversion between values observed from immunohistochemistry (~10% points higher on immunohistochemistry than Western blot in DMD) and those observed from Western blot, but I caution that immunohistochemistry results, in particular, are highly method-dependent, as noted above.
- Rarely, dystrophin levels in the 3 to 10% range have been associated with Becker Muscular Dystrophy phenotypes. Dr. Woodcock found no evidence of a threshold value for protein content and expression of a DMD phenotype.

Despite the absence of reliable data, Dr. Woodcock concluded that evidence from Western blot and other experiments shows 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.

Because of the lack of reliable evidence, I do not agree that the small increase in dystrophin shown in Study 301 is ‘reasonably likely’ to predict clinical benefit. This is the central issue in this appeal.

The “reasonably likely” question hinges on whether the protein is functional, and whether the quantity is adequate.

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Nevertheless, the review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as it does in the Becker form of the disease. Although there can be no certainty on this point, the question of function seems small relative to the uncertainty regarding the adequacy of the quantity of protein, and so function is less germane to the question of “reasonably likely.” In short, it is the quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.

At the outset, it must be stated that the minimum quantity of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown.

There are two ways to consider the quantity of dystrophin produced: as a binary responder analysis and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

The problem with a responder analysis is that there are no data upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Here I provide 3 lines of reasoning to support my view that there is not an adequate basis to believe that the small increase in dystrophin shown in Study 301 is reasonably likely to predict clinical benefit: 1) the treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications; 2) the effect size is inadequate on its face; and 3) no evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.

- 1) *The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications.*

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have considered publications from laboratories that attempt to relate particular levels of Becker-type dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Ideally, as suggested by Dr. Woodcock, there would be reliable data showing that Becker-type dystrophin levels in excess of a particular level are associated with a more benign clinical course.

Realistically however, the use of such a framework would be contingent on the ability to make interpretable cross-laboratory comparisons of dystrophin levels, which would require standardized methods to measure dystrophin levels in muscle specimens. Unfortunately, the methods have differed greatly, and the methods in the literature have lacked critical internal controls such as dilution-series. As stressed above, comparison of dystrophin values across laboratories seems unreliable.

With respect to immunohistochemistry analyses, Figure 2 provides ample basis for concern regarding comparability of results using different methods. Results of separate immunohistochemical analyses of skeletal muscle dystrophin, conducted by the same laboratory on single blocks of tissue, differ by more than an order of magnitude. These results underscore the inherent methodological variability of immunohistochemistry assays, and the futility of attempting to compare dystrophin levels across assays/laboratories.

Even with respect to more recent Western blot methods, reproducibility across laboratories is low. As discussed by Dr. Woodcock, Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. The authors found that variability was particularly pronounced with low levels of dystrophin – precisely the area of interest here.

During the applicants' presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, could not have been more clear in warning us not to make comparisons between their Western blot results and reported data in the literature:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In summary, the field has not achieved adequate standardization of methods for dystrophin quantification at the very low levels observed in eteplirsen-treated patients; therefore, it is not valid to compare an increase in Becker-type dystrophin of, at best, 2 to 3%, with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories. *If the applicant's results cannot be compared to results in historical publications, then there is simply no way to determine whether the low dystrophin levels in eteplirsen-treated patients are reasonably likely to predict clinical benefit.*

2) *The effect size is inadequate on its face.*

If one were to assume that it is possible to make cross-laboratory comparisons of dystrophin levels, the *largest* change reliably demonstrated in Study 301, 1.3%, is an order of magnitude less than the minimum dystrophin levels cited to be important in affecting the course of patients with Becker muscular dystrophy (at least 10%).

Some of the better data come from Van den Bergen *et al*, who studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker Muscular Dystrophy (*J Neurol Neurosurg Psychiatry* 2014; 85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their

patients with dystrophin levels <10% showed poor muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Initially, the applicant reported results from immunohistochemistry analyses purportedly demonstrating that eteplirsen caused 50 to 60% positive staining of muscle fibers for dystrophin. This seemingly unprecedented achievement aroused much excitement in the field of DMD research and in the DMD patient community. Upon proper re-analysis, however, the numbers were far lower, and rigorous statistical analyses showed that the changes weren’t statistically significant. The Western blot analysis from Study 201/202 showed a mean dystrophin level of only 0.93% (range 0 to 2.5%), but these values are of questionable reliability. Finally, an adequate and well controlled study (Study 301) showed a mean change of 3-tenths of a percent (range 0 to 1.3%). Given that dystrophin is a structural protein, it seems highly unlikely that such changes would translate to a clinical effect.

Here are Dr. Woodcock’s assertions on this topic:

“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.”

I agree that broad phenotypic distinctions made in the clinic (e.g., Duchenne vs. Intermediate vs Becker Muscular Dystrophy) are different than trying to predict benefit to an individual patient on the basis of a particular change in dystrophin. And I agree that extending ambulation by 6 months to a year (or similar improvements in other functional areas) would be extraordinarily important.

But Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that “...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.” She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit.

3) *No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.*

Dr. Woodcock states:

“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 nonrandomized 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.”

The review team analyzed the clinical data in great detail, and could not reach the conclusion that there was any reliable evidence of improvement relative to the expected natural history of the disease. Study 201 did not show a treatment effect on its 1° clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients (see my review memorandum for more details).

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD, and their vote was in the face of extraordinary pressure from patients and patient advocates to vote for approval. Two of the 3 “yes” votes were from patient representatives.

Correlation between dystrophin production and clinical effect

A correlation between dystrophin production (or with less certainty – dystrophin *detected*) and clinical function could provide some support for a conclusion that dystrophin production is reasonably likely to predict clinical benefit.

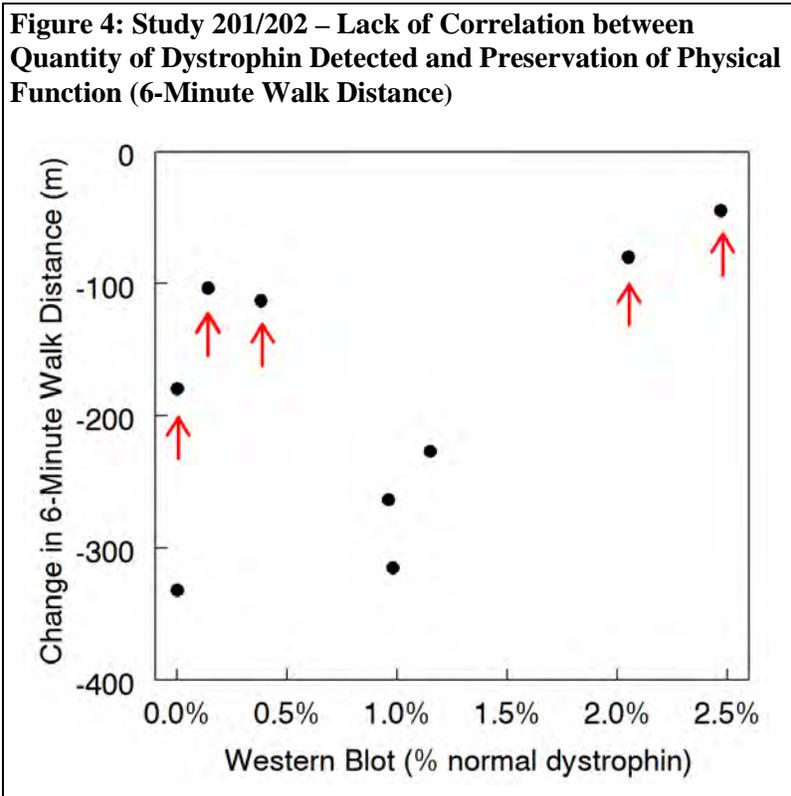
The applicant collected data on both dystrophin production and physical performance in Study 201/202. On the basis of the data presented in the NDA, the Division concluded that no patient in Study 201/202 clearly deviated from the natural history of the disease. The Division reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Thus the Division opined that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

The Division's view notwithstanding, it is worth considering patients on an individual basis to assess the correlation between the quantity of Becker-type dystrophin detected and changes in physical performance.

As noted by Dr. Woodcock, the 6-minute walk test results do not show a strong correlation (Figure 4). For the 9 patients in Study 201/202 who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, the figure shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years.

For the 5 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study (upper right), but 3 had levels that were near-zero (upper left).

Dr. Woodcock also evaluated the North Star Ambulatory Assessment (NSAA) as a function of dystrophin detected in boys who could still walk and who had a dystrophin result at Week 180. She obtained the data from the applicant's briefing document for the Advisory Committee meeting, and found a correlation between dystrophin detected at Week 180 by Western blot and rate of decline in NSAA score through 180 weeks. Her graph is reproduced below:



With respect to the correlation, Dr. Woodcock explained: “This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.”

Given that the correlation was driven by the patient depicted at the lower right (blue arrow; dystrophin level =

~2.5%; change in NSAA = 3), I considered the NSAA data from that patient (Figure 6). I found that his course was less benign than would be inferred from a change in NSAA of only 3 units. Specifically, using linear regression (red line in Figure 6), his NSAA score has, instead, worsened by a mean of 2.7 units per year.

I reasoned that inclusion of all of the NSAA data for each patient would provide a more reliable representation of their course than calculating the change between single pre-treatment and post-treatment data points, because of the test-to-test variability (e.g., short-term swings of 4 to 5 points for patient 006). Thus, using linear regression, I calculated the slope of the relationship between NSAA and time for each patient (as per the red line in Figure 6) and plotted the slopes as a function of the dystrophin detected at Week 180. (Slopes were calculated as loss of NSAA units per year.)

Using this method, there was no correlation ($R^2 = 0.36$), Figure 7. Importantly, the slight trend apparent here is driven by one or two data points.

Figure 5: Study 201/202: Analysis of Change in NSAA vs. Expression of Becker-type Dystrophin by Western Blot (Analysis by Dr. Woodcock)

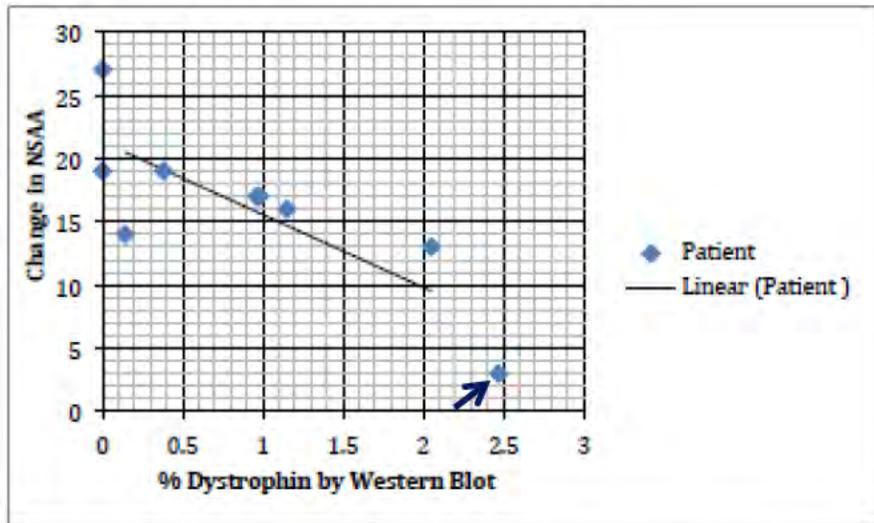
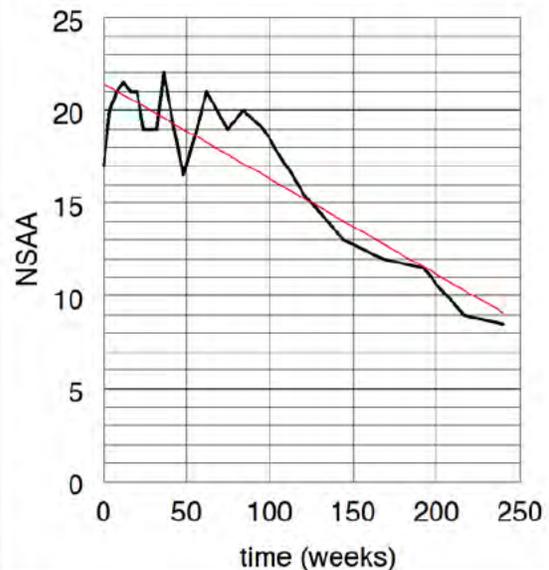


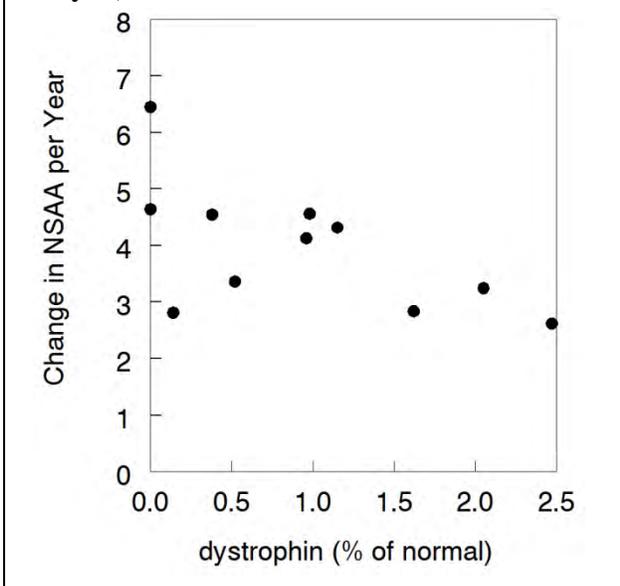
Figure 6: Patient 006: NSAA vs Time



Summary:

In summary, I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%). The levels of dystrophin linked to various Becker Muscular Dystrophy phenotypes in publications are largely not comparable to dystrophin levels measured in this development program. The applicant's interim CEO correctly urged us not to compare data from their Western blot analyses to historical approximations from the literature. And extremely low levels of dystrophin, as found here, seem particularly difficult to quantify and compare across laboratories. Nevertheless, to the degree that findings can be compared across studies, dystrophin levels of 10% or more would need to be achieved to impact the clinical course. The finding in Study 301 is an order of magnitude below this level.

Figure 7: Study 201/202: Analysis of Change in NSAA (Linear Regression) vs. Expression of Becker-type Dystrophin by Western Blot (My Analysis)



Based on protein levels in other deficiency diseases, the effect size here appears to be too small to provide benefit. If dystrophin were an enzyme that catalyzed a biochemical reaction in myocytes, one might posit that a very small quantity could produce a substantial proportion of the minimum necessary reaction product, and that the increase over baseline might be important because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury due to stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. We must also recognize that a treatment that increases dystrophin by 0.3% would seemingly have far less impact than being born with 0.3% more dystrophin, and even *that* seems unlikely to matter.

I can find no precedent of an accelerated approval for a marketing application where the effect size on the surrogate endpoint is as small as 0.3%.

Dr. Woodcock concludes:

“...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....Therefore, I find that the

probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.”

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for demonstration of effectiveness, but this is not true.

Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These facts have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.

Finally, there was no clinical benefit demonstrated in the development program, and the correlation between dystrophin and clinical effect was poor – not surprising given that the applicant provided analyzable data from only 11 patients.

3. Assessment of Possible Impact to Public Health Should My Position Not be Adopted

The approval of this NDA in its present form would have far reaching negative consequences for the public health.

1. Eteplirsen’s risks are certain, whereas its efficacy is not. Having considered Dr. Woodcock’s line of reasoning and her desire to approve eteplirsen, the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs (verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied.

Dr. Woodcock notes that "...the therapy has been relatively safe in the clinic."

The reality is that only a few dozen patients have been exposed to the drug, such that the safety profile is not well characterized. A closely related drug being studied under a (b) (4) With additional experience, important toxicity may emerge for eteplirsen. It is known that many patients in these studies are now receiving infusions through indwelling catheters. Maintenance of vascular access in patients on chronic corticosteroids poses a certain risk of infections. Although we are not yet aware of any infection-related adverse reactions, there would definitely be serious infections and possibly deaths if this drug is marketed, yet evidence of efficacy is lacking.

2. By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

The prospect of providing false hope to desperate patients from a promising but ineffective therapy recalls the experience with *transmyocardial laser revascularization* (TMLR). In the 1990s, patients with coronary atherosclerosis and severe angina who were poor candidates for conventional revascularization procedures ("no-option" patients) underwent a thoracotomy (opening of the chest cavity) to enable use of a laser to create channels through the heart muscle. Ostensibly, these channels provided conduits for blood to flow from inside the left ventricle to the myocardium. Conduct of sham-controlled studies was impossible; studies were essentially baseline-controlled or historically-controlled. Large treatment effects were reported by a number of investigators, generally from small studies. There were marked increases in treadmill exercise time and relief of angina, with effects sustained for more than a year in some cases. Although many in the cardiology community raised concerns about expectation bias and were highly skeptical of the results, to some the effects seemed larger and more durable than could possibly be explained by expectation bias, i.e., a placebo effect. Thousands of patients underwent this invasive procedure with the hope of angina relief. Some years later, with improvements in technology, the conduct of sham-controlled studies became feasible, and TMLR was not found to be effective. The false hope was ultimately dispelled with the publication of two Cochrane Reviews.³ These reviews found the appearance of a marked treatment effect, but 30-day mortality was 6.8% in the TMLR group vs. 0.8% in the no-treatment group. They noted "The assessment of subjective outcomes, such as improvement in angina, was affected by a high risk of bias and this may explain the differences found." In this case, the cost of false hope was ~6% mortality in the first 30 days post-op.

I will also note that the primary endpoint of these laser studies was generally exercise capacity – the same type of endpoint used in the eteplirsen DMD development program, also for "no option" patients.

3. The accelerated approval pathway is designed to expedite the availability of promising new therapies to patients with serious conditions, especially when there are no satisfactory

³ Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003712. DOI: 10.1002/14651858.CD003712.pub3

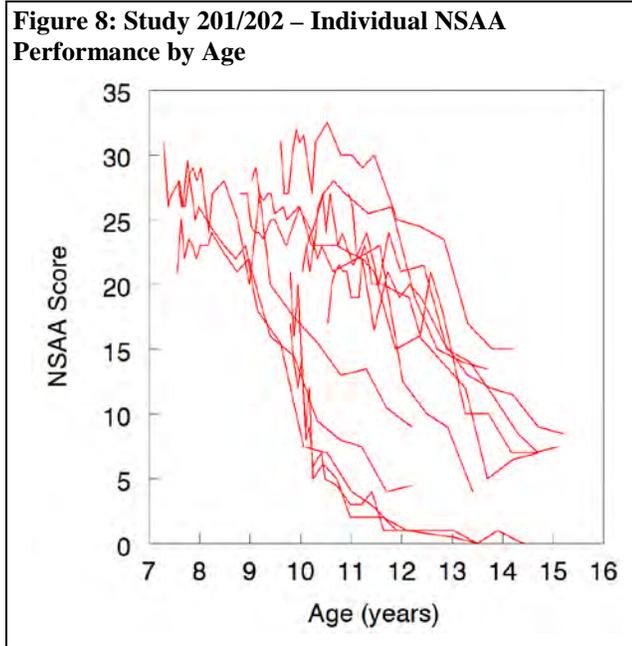
alternative therapies, while preserving standards for safety and effectiveness. For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit, and FDA may withdraw approval of a drug if a trial required for verification of the predicted clinical benefit fails.

In reality, it is difficult to withdrawal a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options. FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval. The reality is that if eteplirsen is given accelerated approval, it is highly likely to remain on the market indefinitely, irrespective of whether or not efficacy is verified.

4. With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression.
5. False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually *are* effective. For example, consider the scenario of a related drug with far greater potential to promote dystrophin production in patients with DMD. In order for a sponsor to study such a drug, patients would likely have to agree to discontinue eteplirsen, and few patients may be willing to do so. In short, approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective, and this impact can be significant.
6. Accelerated approval would lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered “reasonably likely” to support accelerated approval. Similarly, if a ‘responder’ had been defined as a patient with an increase in dystrophin of $\geq 1\%$ (and there is no basis to accept such a low threshold), there would have been only a single responder in Study 301. If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.
7. With accelerated approval of this NDA, there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of

failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.

8. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, we already know this dose is sub-therapeutic. We know this because patients who have been receiving this eteplirsen dose for some 3.5 years have been progressing at a rate that is similar to that expected, based on the natural history of the disease (Figure 8). I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic, when the consequence of a sub-therapeutic dose is clinical deterioration and death. The figure shows the unremitting progression in the patients in Study 201/202, based on changes in NSAA.



9. Approval of this NDA would send the signal that political pressure and even intimidation – not science – guides FDA decisions, with extremely negative consequences (See Grainger D., 11/30/15. “DMD Drugs: an existential threat to FDA,” *Forbes*⁴). The public is well aware of this development program: the meager size of the study population, the marginal (at best) effect size, the Division’s dim view of the efficacy data, and the robust activism of some members of the DMD community. Many would be amazed at an approval action, because other DMD drugs, recently turned down for approval, appeared to provide stronger evidence of efficacy.

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

“Dear Dr. califf: How is it that everyone in and around DMD understands this simple Idea and the science geniuses at FDA don't? You stupid f__ _ers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

⁴ downloaded 7/18/16 at <http://www.forbes.com/sites/davidgrainger/2015/11/30/dmd-drugs-an-existential-threat-to-the-fda/#5ffc712455f7>

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

4. Detailed Description of the History of the Dispute, Including My Description of the Center SDR Procedures Followed and/or Not Followed, Dates of Meetings, and Decisions Rendered Throughout the Process

The following table shows the dates and main activities for 15 Center Director Briefings associated with the development of this drug: 8 Center Director Briefings took place during the IND phase of development, *prior to submission of the NDA*, and 7 Center Director Briefings took place during review of this NDA.

DATE	MEETING	DETAILS
7/17/2013	Center Director Briefing	Follow up on Action Item from 3/13/13 EOP2 Meeting: Sarepta has submitted a comprehensive discussion of the issues from the EOP2 mtg. To discuss the suitability to file the NDA for Subpart H approval.
10/18/2013	Center Director Briefing	Dr. Unger presented an overview and Dr. Farkas had a slide presentation on drisapersen and eteplirsen data. Discussion: 1. Plan to have a manufacturing facility visit by ONDQA - to observe process and obtain yield calculation. Sponsor is expecting to have 2nd batch in Dec 2013. Determine how much product the sponsor has. 2. OBP: recommended to establish specificity of the antibody and variability of the assay. 3. Next trial - plan to have OSI group to observe the conduct. 4. Need data from the GSK (drisapersen) trial. DNP has previously requested the Phase 3 topline data from GSK, but did not get any response. Dr. Woodcock will initiate an inquiry to the sponsor (raw data). 5. The Agency needs to assist Sarepta (characterize biomarker, CMC facility, observe 6MWT, etc.) 6. 2nd Internal Meeting (Drs. Woodcock, Temple, Jenkins, Unger and Neuro) before the 11/8/13 sponsor meeting. Discuss further what to convey to Sarepta.
10/28/2013	Center Director Briefing (continuation of 10/18/13 meeting)	Suggestions/Recommendations for DNP to Consider: -- We have concluded that we will not ask for biopsy until (we understand the histopathology and are) we're certain what is a quantitative measure and identified the surrogate marker for the study. -- Tell the sponsor that we have changed our view for the quantitative measure of truncated dystrophin as a surrogate PD marker used in their study, because of the recent natural history

		<p>study and failure of the drisapersen trial from GSK.</p> <p>-- Dr. Woodcock wants to have a comprehensive literature review to fully understand what's this mean of the deletions, mutations, or duplications in the dystrophin gene, or this exon 51 of dystrophin mRNA ((Office of Translational Science) believe this task was assigned to a different group).</p> <p>-- To ask the Sponsor to provide their production schedule. I believe Dr. Woodcock wants to understand the amount of production and determine if the company can provide the drugs to those DMD patients in the future.</p> <p>-- To suggest that the Sponsor consider enrolling patients younger in age (like starting with 5yrs) in their clinical study.</p> <p>-- To ask the Sponsor if they could provide drugs for compassionate use to patients (who are very sick or those were in the drisapersen trial previously).</p> <p>-- Schedule a T-con with GSK to discuss biomarker data</p>
1/17/2014	Center Director Briefing	Request: Team to present DMD drugs study design to Dr. Woodcock – Path forward for Sarepta (& GSK)
2/6/2014	Center Director Briefing	DMD drugs study design (Discuss Sarepta path forward) Action items: (a) Request biomarker data from the sponsor - done TC on 2/7/14(b) If data interpretable, meet with sponsor for a brainstorming session. Then follow-up with Advice Letter
3/5/2014	Center Director Briefing	Dr. Ash Rao presented biomarker data findings (including Drs. Woodcock, Jenkins, Temple, Unger, Moscicki) Team discussed path forward. Action Item: to invite Sarepta for a brainstorming discussion.
3/19/2014	Sponsor Meeting, with Center Director	brainstorming discussion - study design and path forward Action: Sarepta to submit proposed studies and next steps
4/2/2014	Center Director Briefing	Drs. Woodcock, Moscicki, Temple, Unger Discuss proposal & comments to sponsor ~Advice Letter-include previous meeting discussions ~FDA workshop – biomarker ~Work w/ sponsor on dystrophin biomarker ~Natural history raw data - primary investigators
6/26/2015		SUBMISSION OF NDA
12/9/2015	Center Director Briefing	To brief on the current status of eteplirsen review in advance of the planned Jan 22, 2016 AC meeting. To discuss the application and the plan of action.
1/13/2016	Center Director Briefing	To review the slide presentation and plan of action for eteplirsen, that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership.
2/10/2016	Center Director Briefing	To discuss the ongoing review of the NDA, and what will be presented during the Advisory Committee Meeting in April. To discuss the strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.
4/15/2016	Center Director Briefing	To discuss the statistical review of the CINRG data. To discuss the review of data on DMD that was conducted by the Cooperative International Neuromuscular Research Group
4/25/2016	Advisory Committee Meeting	
5/4/2016	Center Director Briefing	Discuss the outcome and plan of actions for the application post advisory committee meeting

5/31/2016	Center Director Briefing	Discuss reviews conducted by the review team and leadership along with any additional information obtained from the sponsor. Discussed Dr. Woodcock's memo. Timeline for reviews due to Dr. Woodcock.
7/6/2016	Center Director Briefing	<ol style="list-style-type: none"> 1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be "reasonably likely to predict clinical benefit" and used as a surrogate endpoint to support accelerated approval. 2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval. 3. Description of the available clinical data in the drug label if approved.

Based on my years of experience in Office of Drug Evaluation-I, the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented. She also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.

There is no question that there has been adequate time and place for the discussion of various views. I will note, however, that I found it unfortunate that the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already "...reached a different conclusion...." than the review team.

5. Action, Decision or Remedy Sought

Although the above paragraph could be considered grounds for an appeal based on process, I seek instead a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit. I maintain, along with the Division of Neurology Products, Office of Biometrics, Office of Clinical Pharmacology, Office of New Drugs, and the majority of the members of the Peripheral and Central Nervous System Drugs Advisory Committee, that substantial evidence is lacking to support either a conventional or accelerated approval, and that a *complete response* should be issued for this NDA.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will eventually be capable of ameliorating the fundamental genetic defect of DMD, but the effect size here is insufficient at the tested doses.

6. Path Forward

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at doses of 30 and 50 mg/kg/week are fairly solid, but they do not support efficacy.

I remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the primary endpoint, again, testing higher doses.

The applicant is continuing to enroll Study 301 (PROMOVI), an open-label, multicenter, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

My suggestion for a path to approval is to randomize patients in the ongoing Study 301 to:

- 1) either remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blinded to treatment group. For accelerated approval, the primary endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the primary endpoint would be a test(s) of physical performance such as NSAA or rise time.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, would want to know whether higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients randomized to placebo, this would not be a concern here with all patients receiving active drug. And I would recommend that the applicant forego immunohistochemistry studies in favor of Western blot analyses, such that needle biopsies with local anesthesia would be sufficient (rather than open biopsies with more intensive anesthesia and greater morbidity).

I also believe that it would be desirable for the company to provide access to eteplirsen for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.



Date: August 8, 2016

To: Robert Califf, M.D.
Commissioner of Food and Drugs

From: Luciana Borio, M.D. Luciana Borio -
Acting Chief Scientist A Deputy Associate Commissioner,
Office of Food Safety, Center for
Drug Evaluation and Research,
U.S. Food and Drug Administration

Subject: Scientific Dispute Resolution Appeal regarding Eteplirsen

This matter is before the Office of the Commissioner on an appeal submitted by Ellis Unger, M.D., Director of the Office of Drug Evaluation I (ODE-I) (the initiator), under Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA" (the SDR-SMG). In his scientific dispute resolution (SDR) appeal, dated July 18, 2016, Dr. Unger challenges the basis for a decisional memorandum issued by Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research (CDER). Dr. Woodcock's decisional memorandum concludes that a new drug application (NDA) submitted by Sarepta Therapeutics Inc. (Sarepta) for eteplirsen, a drug intended to treat Duchenne muscular dystrophy (DMD), meets the standard for accelerated approval under 21 CFR § 314.510. Specifically, Dr. Woodcock's memorandum states that the data submitted in support of the NDA establishes "increased dystrophin protein production, a surrogate endpoint [for DMD] that [she] conclude[s] is reasonably likely to predict clinical benefit."¹ Dr. Unger states that he disagrees with Dr. Woodcock's decisional memorandum because he does not believe "the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit."²

Upon receipt of the appeal from Dr. Unger, in accordance with the SDR-SMG, the Office of the Chief Scientist convened the Agency Scientific Dispute Process Review Board (the SDR Board), a standing committee, which I chair, whose role in evaluating the appeal is to conduct a review of the processes used in the Center to render a decision on the scientific dispute at issue.³ Under the SDR-SMG, "The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."⁴ My role in the process, as Chair of the SDR Board, is to provide a recommendation to you, as Commissioner of Food and Drugs, with respect to "whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or concerns; [whether] all relevant evidence bearing on the scientific question at issue has been considered; and[] whether the dispute should be remanded to the Center Director."⁵ The written

¹ Woodcock Decisional Memorandum at 1.

² Appeal at 3.

³ SDR-SMG at 3. ("The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist.")

⁴ *Id.* at 12.

⁵ *Id.* at 5.

recommendation must reflect the SDR Board's underlying rationale, along with minority views among the members, for those findings.⁶

In conducting its evaluation, the SDR Board reviewed pertinent aspects of the Center's administrative file for the eteplirsen NDA and interviewed Dr. Unger, Dr. Woodcock, one member of the review team for the NDA, who requested anonymity, and Virginia Behr, the Ombudsman for CDER. Based on its review, the SDR Board has determined that the processes followed by CDER provided Dr. Unger with an adequate opportunity to present his scientific views and that CDER considered all relevant evidence. As Chair of the SDR Board, I therefore recommend that you do not remand this matter to the Center Director for further action.⁷ However, there are additional considerations meriting your attention, which I describe below. Furthermore, the SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit.

BACKGROUND

1. *Eteplirsen and DMD*

Dr. Unger provides an overview of eteplirsen and DMD in his appeal.⁸ In short, DMD is a genetic disorder with catastrophic effects on its sufferers:

[DMD] is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene[,] . . . [which] disrupt the messenger ribonucleic acid (mRNA) reading frame [and] lead[] to the absence or near-absence of dystrophin protein in muscle cells. . . . Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. . . [and a concomitant] loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.⁹

There are no FDA-approved therapies for DMD.¹⁰ Sarepta has designed eteplirsen to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded from the resulting mRNA:¹¹

[B]y restoring [] the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug

⁶ *Id.* at 13.

⁷ *See id.* ("The Commissioner will review the [SDR Board's] recommendation and render a final decision on . . . whether the dispute should be remanded to the Center Director for corrective action" and "work with the Center Director to determine what corrective actions must be taken, if any.").

⁸ Unless otherwise indicated, Drs. Unger and Woodcock appear to agree as to the background provided in this section.

⁹ Appeal at 2.

¹⁰ *Id.*

¹¹ The charity, Muscular Dystrophy UK, has a nice description of the technology underpinning eteplirsen, which can be accessed at: <http://www.muscular dystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/>.

would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.¹²

In attempting to establish that eteplirsen is safe and effective for the treatment of DMD, and thus meets one of the standards for approval in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Sarepta has submitted data from three clinical studies:

Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study.¹³

Dr. Unger further explains:

The endpoints for [the three] studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.¹⁴

Immunohistochemistry (IHC) analysis looks at thin slices of muscle biopsies to see if dystrophin is present or absent. Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. Western blot analysis assesses how much dystrophin is present.

For Study 201/202, Sarepta submitted Western blot and IHC analysis evaluating proteins in muscle samples obtained from the twelve patients before the study and then again at twelve, 24, and 48 weeks.¹⁵ “The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.”¹⁶ Because CDER also determined that the conditions under which the original IHC analysis was performed were inadequate, including that the reader was not masked to sequence and time, the Center requested a re-reading of the stored images by three masked pathologists under different conditions.¹⁷ The IHC results from the reread were not nearly as favorable, as compared to the initial IHC results reported by Sarepta.

¹² Appeal at 2.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.* at 4, 8.

¹⁶ *Id.* at 4.

¹⁷ Unger Decisional Memorandum at 12-13.

The re-read showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group[] (. . . [T]he type-I error rate was not controlled for multiplicity.)¹⁸ Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.¹⁹

For Study 201/202, CDER also worked with Sarepta to improve the Western blot assays, and researchers performed repeat biopsies on eleven of twelve patients at Week 180.²⁰ Only three of the eleven patients had stored baseline samples that were adequate for evaluation, and so baseline samples were obtained from six additional patients external to Study 201/202.²¹ Dr. Unger also notes that all baseline samples were obtained from a different muscle group than the samples obtained at Week 180.²² Based on its own analysis of the IHC data, Sarepta claimed a remarkable increase of dystrophin immunostaining at Week 180: from 1.1% ± 1.3% positive muscle fibers at baseline to 17.4% ± 10.0% positive fibers at Week 180.²³ The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers.²⁴ Dr. Unger remarked that the lack of concordance between the IHC and the Western Blot results is “striking” and also noted that FDA did not verify the integrity of the IHC results.²⁵ As previously noted, each muscle fiber that shows any amount of dystrophin is counted as positive in IHC, regardless of the actual quantity of dystrophin present.

As noted above, Study 301 is an ongoing study. For purposes of its review of the NDA, CDER requested that Sarepta perform Western blot analysis on samples obtained from 13 patients enrolled in the study.²⁶ The analysis compared paired biceps samples: baseline samples and samples obtained at 48 weeks, after 48 weeks of treatment with 30 mg/kg of eteplirsen infusion.²⁷ Dr. Woodcock told the SDR Board that representatives from CDER were present in the laboratory for the Western blot analysis and oversaw the procedures and controls. The Western blot analysis showed a statistically significant increase in dystrophin, ranging in an increase from 0.22% to 0.32% of normal.²⁸ It should be noted, however, that a statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit, which is the issue at the core of Drs. Unger and Woodcock’s scientific disagreement.

¹⁸ That is, with respect to time points of assessment and the 2 doses tested.

¹⁹ Appeal at 8-9. Of note, in her decisional memorandum, Dr. Woodcock rejected the findings in both the original and second evaluation of the images: “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.” (Woodcock Decisional Memorandum at 2). She explained to the SDR Board that, after consultation with others in CDER, she does not view IHC results standing alone as a valid method to evaluate dystrophin levels.

²⁰ Appeal at 5.

²¹ *Id.* at 5, 9.

²² *Id.* at 5. Dr. Unger clarifies in his decisional memorandum that the baseline biopsies were from the biceps muscle, the Week 180 biopsies from the deltoid muscle. (Unger Decisional Memorandum at 17).

²³ Appeal at 9. As discussed below, however, Dr. Unger does not believe that those results are reliable.

²⁴ *Id.* at 5.

²⁵ *Id.* at 9-10.

²⁶ *Id.* at 6. Dr. Unger states that the biopsies were obtained from 13 patients but only reports the data as to 12 patients. “There was one patient for whom none of the values met the acceptance criteria [for the Western blot assay].” (Unger Decisional Memorandum at 21).

²⁷ Appeal at 6.

²⁸ *Id.*

2. *Legal Standard for Accelerated Approval and Patient Perspectives*

On December 11, 1992, on the basis of its broad statutory authority to approve drugs under the FD&C Act, FDA issued regulations providing for accelerated approval of drugs.²⁹ Under 21 CFR § 314.510, FDA may grant accelerated approval for a drug based on a surrogate endpoint under certain circumstances:

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on **a surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.³⁰

The preamble to the proposed rule defines “surrogate endpoint” as follows:

A surrogate endpoint, or “marker,” is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.³¹

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 901 of FDASIA amended the FD&C Act to provide FDA with specific authority to grant accelerated approval to drugs for serious conditions.³² Section 506(c) of the FD&C Act now largely tracks language in the regulations issued by FDA in 1992. Section 901 of FDASIA also added current section 506(e) to the FD&C Act, which clarifies that the amendments were “intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval” but that “[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d) of [the FD&C Act].”³³

Section 901 of FDASIA also directed FDA to issue guidance to industry on the development of

²⁹ 57 Fed. Reg. 58942 (Dec. 11, 1992).

³⁰ Emphasis added.

³¹ 57 Fed. Reg. 13234, 13235 (Apr. 15, 1992).

³² FDASIA, PL 112-144, July 9, 2012, 126 Stat. 993.

³³ *Id.*

drugs for accelerated approval and required consideration of the following:

In developing the guidance . . . [FDA] shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.³⁴

Section 1137 of FDASIA further directs FDA to:

develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.³⁵

In May 2014, FDA finalized a guidance on “Expedited Programs for Serious Conditions — Drugs and Biologics.” The Guidance provides general information on the evidence that the agency considers in determining whether to grant accelerated approval.³⁶ The Guidance clarifies that assessing a surrogate endpoint hinges on understanding both the disease process and the relationship between the drug’s effect and the disease process.³⁷ With respect to the latter, the Guidance states:

The extent to which a drug’s effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically[,] but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome.³⁸

The Guidance also provides some insight on how the agency exercises its judgment in evaluating surrogate endpoints when little is known about how an effect on a surrogate endpoint might affect clinical endpoints:

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.³⁹

³⁴ *Id.*

³⁵ *Id.*

³⁶ Expedited Programs Guidance at 19-22.

³⁷ *Id.* at 20-22.

³⁸ *Id.* at 21.

³⁹ *Id.* at 21-22.

FDA obtains patient perspectives through a variety of avenues, “such as open public hearings on specific diseases or drug development issues, and as speakers at FDA-sponsored conferences and workshops.”⁴⁰

3. *SDR-SMG and CDER’s SDR-SOPs*

The Office of the Commissioner issued the SDR-SMG on January 13, 2009. Its stated purpose is “to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency.”⁴¹ The SMG “encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders” and cautions that the “agency’s appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.”⁴² As noted above, the SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals. Under the SDR-SMG, the SDR Board evaluates whether “the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”⁴³ As Chair of the SDR Board, the Chief Scientist then provides a written recommendation on those issues to the Commissioner, who renders a final decision on whether the scientific dispute should be remanded to the Center for further action.⁴⁴

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency’s “requirements for the minimum standards for scientific dispute resolution processes in the Centers” and provides a collection of non-mandatory “best practice[s]” for such dispute resolution.⁴⁵ The SDR-SMG’s requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.⁴⁶

The SDR-SMG then goes on to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes (SDR-SOPs) in the event that such informal attempts at resolution are unsuccessful.⁴⁷ In contrast to the procedural review contemplated by

⁴⁰ 79 Fed. Reg. 65410, 65411 (Nov. 4, 2014).

⁴¹ SDR-SMG at 1.

⁴² *Id.* at 2.

⁴³ *Id.* at 12.

⁴⁴ *Id.* at 12-13.

⁴⁵ *Id.* at 2-3.

⁴⁶ *Id.* at 6.

⁴⁷ *Id.*

the SDR-SMG, Center-level SDR-SOPs should provide for substantive review of the scientific disputes at issue within the Center.⁴⁸

At CDER, there are three interrelated chapters of the Center’s Manual of Policies and Procedures (MAPPs) that serve to implement the SDR-SMG’s requirements. The first, MAPP 4151.8, “Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions,” sets forth CDER’s principles for resolving scientific disputes informally and requires “a collaborative environment for decision-making.”⁴⁹ According to the MAPP, “[s]uch an environment requires open communication and exchange of ideas in a mutually respectful professional environment[] and the full and open participation of all relevant disciplines and organizational components in the decision-making process.”⁵⁰ MAPP 4151.8 states that “[e]ach individual who contributes to the decision-making process” must “be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component” and that “[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made.”⁵¹

The second and third MAPPs at issue directly relate to CDER’s formal SDR process. MAPP 4151.1, “Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain,” provides for raising a scientific issue to the “Next Highest Management Official” (NHMO) if alignment on an issue cannot be reached by the staff on a team or through discussions with a team leader or first-level supervisor. The individual who disagrees with the decision (the disputant) “. . . may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees . . . as well as the proposed changes and rationale for the changes in recommendations and/or conclusions.”⁵²

The disputant submits the statement to the NHMO, i.e., “the management official one level above the management official who made the decision being disputed.”⁵³ The NHMO then issues a written decision on the issue, and any disputant may then appeal the written decision up the chain of command all the way to the Center Director through use of the same process.⁵⁴ MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director,” provides for further formal review under certain circumstances if alignment cannot be reached under the process in MAPP 4151.1.⁵⁵ A CDER employee may initiate the process by submitting a written package, which must include “[a]n assessment of the possible significant negative consequences to the public health” at issue in the dispute, to the CDER Ombudsman.⁵⁶ The CDER Ombudsman and the Center Director then “determine whether the consequences of the decision in question are potentially serious enough to warrant” additional review.⁵⁷ If so, the Center Director appoints a chairperson to lead an *Ad Hoc* review panel for purposes of evaluating the scientific dispute and providing a recommendation to the Center

⁴⁸ See *id.*; see also footnote 136.

⁴⁹ MAPP 4151.8 at 2.

⁵⁰ *Id.*

⁵¹ *Id.* at 2-3.

⁵² MAPP 4151.1 at 3.

⁵³ *Id.*

⁵⁴ *Id.* at 4.

⁵⁵ *Id.* at 5; MAPP 4151.2 at 1-2.

⁵⁶ MAPP 4151.2 at 5.

⁵⁷ *Id.*; see also *id.* (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted . . .”).

Director, who renders the final decision.⁵⁸ The *Ad Hoc* panel typically includes one member with relevant technical expertise, one member chosen from a list provided by the person requesting review, and, if possible, one member with relevant expertise who is external to the agency.⁵⁹

4. Procedural History of the Dispute in CDER

Sarepta submitted its NDA for eteplirsen (#206488) on June 26, 2015.⁶⁰ CDER assigned it for review to the Division of Neurology Products (DNP) within ODE-I, the office for which Dr. Unger serves as Director.⁶¹ Even before submission of the NDA, however, representatives from the Office of New Drugs (OND), DNP and ODE-I (the review team) regularly briefed Dr. Woodcock on issues related to the ongoing study of eteplirsen pursuant to an investigational new drug application (IND) and the anticipated NDA.⁶² The discussions at these briefings included among their topics: the suitability of eteplirsen for accelerated approval, an overview and background for eteplirsen, study design, a clinical site inspection report for Sarepta, general brainstorming, and planned communications.⁶³ Dr. Unger told the SDR Board both that there were far more briefings of the Center Director than is typical and that the scope of those briefings included an unusual level of detailed discussion.

During the SDR Board's separate interviews of Dr. Unger and the review team member (RTM), the SDR Board learned that, at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions—anywhere from six to twelve times—from very early on in the review process. The RTM described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as “intense,” “personal,” and “intimidating.” Dr. Unger and the RTM both thought that Dr. Woodcock's early interest and involvement in DNP's approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community in relation to an article published about the initial findings for Study 201/202, which Drs. Unger and Woodcock now agree are misleading and unreliable. Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that OND has been very conservative in evaluating drugs for accelerated approval. In his decisional memorandum, Dr. Unger explains the excitement surrounding eteplirsen at the time as follows:

[The initial findings for Study 201/202] were substantially reported in a 2013 publication, which claimed that eteplirsen markedly increased functional dystrophin production: “...*the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients (p≤0.002). Even greater increases occurred at week 48 (52% and 43%*

⁵⁸ *Id.* at 6-7.

⁵⁹ *Id.* at 6.

⁶⁰ Unger Decisional Memorandum at 1.

⁶¹ *Id.* at 2.

⁶² Appeal at 24-25; Chronology prepared by Virginia Behr and submitted to the SDR Board (Behr Chronology) at 1-2. In his appeal, Dr. Unger consistently refers to the representatives from OND, OND-I and DNP who were involved in the review of the eteplirsen NDA as the “review team” or as “the division,” even though he appears to be referring to senior management within OND on occasion. Dr. Woodcock has also used the same terminology on occasion, though not as consistently. For the sake of efficiency, this memorandum refers to everyone at CDER who was involved in the review of the eteplirsen NDA, besides Dr. Woodcock herself, as the review team. Nonetheless, the SDR Board notes that, within FDA, “review team” is often used to reflect the core team of individuals within a division who are directly engaged in the review of the science underlying a regulatory submission.

⁶³ Appeal at 24-25; Behr Chronology at 1-2.

in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

Publication of this paper was followed by a Sarepta press release, which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community.⁶⁴

In their interviews with the SDR Board, Dr. Unger and Dr. Woodcock stated that FDA also received significant correspondence from the public and Congress, much of which urged approval of eteplirsen.⁶⁵ Some of the correspondence used vulgar language and was abusive to the review staff.⁶⁶

The briefings of Dr. Woodcock began again five to six months after submission of the NDA for eteplirsen.⁶⁷ The focus of these briefings was on preparation for a planned meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC meeting) to provide advice on the review of the eteplirsen NDA, which meeting was initially scheduled for January 2016 but then rescheduled for April 25, 2016.⁶⁸ The preparation involved discussions of the ongoing review of the data, including the “strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.”⁶⁹ During their respective interviews with the SDR Board, both Dr. Unger and the RTM conveyed their belief that Dr. Woodcock was inclined to grant approval from very early on in the process. But the RTM stated that Dr. Woodcock’s views were not always clear during discussions throughout the review of the science—sometimes she seemed to agree with external constituents, sometimes not. The RTM told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged DNP to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases). The RTM highlighted to the SDR Board that at least two members of the review team were leaving FDA or had left the agency in the wake of both the decision-making process within CDER and the pressures exerted by outside forces.

Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014. She said that her goal throughout the discussions

⁶⁴ Unger Decisional Memorandum at 11 (emphasis in original), citing Mendell JR, *et al*: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47 and Sarepta press release, dated 8/8/13 (<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irolnewsArticle&ID=1846052>). Dr. Unger also notes, “It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible.” Unger Decisional Memorandum at 11.

⁶⁵ See also Appeal at 23.

⁶⁶ See, e.g., *id.* at 23-24.

⁶⁷ *Id.* at 25; Behr Chronology at 2-3.

⁶⁸ Appeal at 25; Behr Chronology at 2-3.

⁶⁹ Appeal at 25.

with the review team was to convince them to come around to her more flexible way of thinking about the data. According to Dr. Woodcock, she recognized that there were serious and significant flaws in the study design for Study 201/202 and the data it generated but that she did not “want to hold” those flaws “against the patients.” She conceded that the results produced by Studies 201/202 and 301 were always less than anyone in CDER had hoped.

In their respective interviews with the SDR Board, both Dr. Unger and the RTM focused to some extent on Dr. Woodcock’s involvement in the planning stages for the AC meeting. They expressed some surprise at the extent of her involvement. Dr. Unger indicated in his interview with the SDR Board that Dr. Woodcock even advocated, unsuccessfully, for changing the order of the questions to be posed to the committee and wanted the question on conventional approval to come before the one on accelerated approval.

The RTM told the SDR Board: (1) that Dr. Woodcock made it clear in one or more of the meetings leading up to the AC meeting that she intended to speak at the meeting but (2) that the substance and purpose of her participation were never communicated. Although the RTM affirmatively stated that the review team was free to develop its own presentation to the committee, uncertainty with respect to Dr. Woodcock’s role made doing so more difficult. The RTM also noted that Dr. Woodcock requested a longer than is typical Open Public Hearing portion of the AC meeting that, as a result, the review team thought there would insufficient time for them to make their presentations during a one-day meeting. The RTM stated that the review team asked to extend the advisory committee to two days but that they were overruled.

On April 25, 2016, CDER held the AC meeting. The meeting focused on the data from Study 201/202.⁷⁰ Dr. Woodcock spoke at the meeting several times. At the meeting she made a presentation that was intended to “provide a framework within which to consider [the] data [underlying the eteplirsen NDA] based on [her] 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval.”⁷¹ She highlighted many of the difficulties in interpreting the data.⁷²

At the AC meeting, Dr. Woodcock also described the standards for both conventional and accelerated approval of drugs but mentioned that the agency had not “articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit.”⁷³ She concluded her presentation with the following remarks:

I would note that much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective.

There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally [] have little say in how the standards are implemented.

The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you've heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent

⁷⁰ Sarepta had not yet submitted the data from Study 301.

⁷¹ Advisory Committee Transcript at 151.

⁷² *Id.* at 151-155.

⁷³ *Id.* at 155-156.

presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated initially and that in fact sometimes we will collectively get it wrong, otherwise accelerated approval would really have no different standards than regular approval.⁷⁴

During the questions to the committee members, Dr. Woodcock restated the standard for accelerated approval and emphasized that, with regard to the surrogate endpoint of dystrophin, there has never been a “threshold established [to show a reasonable likelihood of predicting clinical benefit] because there's never been a drug to do this.”⁷⁵ When later asked for clarification of the extent to which the committee members were to incorporate the testimony of the boys and their families into their evaluation of clinical outcomes for Study 201/202, Dr. Woodcock stated:

Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk. * * * So the statutory standard is more or less as described there, but there is flexibility, and that's where we should take the views of the community into account.⁷⁶

During his SDR Board interview, the RTM stated that, notwithstanding Dr. Woodcock's emphasis on accelerated approval and the standard of “reasonably likely to predict clinical benefit,” “[s]urrogacy was not discussed in any genuine scientific way” during the AC meeting because it had not been framed that way by Sarepta through its presentation to the committee. The RTM specifically stated that there was no discussion of “substantial evidence” in the context of accelerated approval, nor what might constitute “interpretable evidence.” The RTM believed that, by the end of an emotional AC meeting, the framework for evaluating the data under the appropriate regulatory standards, as provided by the review team toward the start of the meeting, had been forgotten by the committee members.

Dr. Woodcock explained to the SDR Board that she thought both that the review team did a poor job framing the issues during their presentations and that the questions were confusing and poorly worded. Indeed, during her interview with the SDR Board, Dr. Woodcock opined that the review team “did not put its best foot forward.” She speculated that the confounding factor was the number of interested persons attending both in person and by webcast. She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen. She thought that the review team's presentation of the IHC data, in particular, was confusing. She further opined that the review team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand. Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates.

At the conclusion of the AC meeting, the committee voted against accelerated approval by a margin of 7-6.⁷⁷ Three of the members who voted in favor of accelerated approval were the consumer representative and the two patient representatives.⁷⁸

⁷⁴ *Id.* at 158-59.

⁷⁵ *Id.* at 484.

⁷⁶ *Id.* at 548-549.

⁷⁷ *Id.* at 486-95.

⁷⁸ *Id.* at 2-7, 486-88.

On May 4, 2016, Dr. Woodcock met with the review team to discuss the AC meeting and plan of actions for the NDA.⁷⁹ In his appeal, Dr. Unger contends that Dr. Woodcock “made clear her intent to approve the drug” at this meeting, even though she had not yet reviewed drafts of DNP’s final review memorandum or his review memorandum.⁸⁰ According to Dr. Unger, Dr. Woodcock explained that she had already “reached a different conclusion” than the review team.⁸¹ Dr. Woodcock explained to the SDR Board that the memoranda were discussed during the Center Director briefings and that she felt she understood the views of the review team and did not see the point of an “exchange of reviews.”

On May 24, 2016, Dr. Unger met privately with Dr. Woodcock to discuss the eteplirsen decision.⁸² On May 31, 2016, Dr. Woodcock met with representatives from the review team to discuss their reviews and her initial draft of a decisional memorandum based primarily on the data from Study 201/202.⁸³ Dr. Woodcock received comments back from the review team at the same meeting.⁸⁴ Dr. Unger told the SDR Board that he and members of the review team—including Dr. Robert Temple, Deputy Center Director for Clinical Science and Dr. John Jenkins, Director of OND—discouraged Dr. Woodcock from finalizing the decisional memorandum and granting accelerated approval for eteplirsen until the additional data from Study 301 could be obtained.

On June 3, 2016, in response to an email from Sarepta, a letter signed by Dr. Woodcock issued to the sponsor.⁸⁵ The letter requested the additional data from Study 301, which was to include comparisons of any biopsy samples obtained at Week 48 to the respective baseline samples for those patients.⁸⁶ The letter stated,

If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).⁸⁷

Dr. Woodcock explained that Dr. Unger and the review team essentially agreed to the timeframe of four business days, though they pushed instead for six. She felt that there was general agreement that data from only twelve patients could be reviewed quickly, especially given that representatives from CDER would be overseeing the Western blot analysis and ensuring that it was done properly.

On June 27, 2016, Sarepta submitted the requested data.⁸⁸ Dr. Woodcock explained that accelerated approval was not granted within four business days of that date precisely because the results of the analysis were disappointing in that they provided evidence of only a minimal increase in dystrophin at 48 weeks. Dr. Unger sent an email to Dr. Woodcock that read:

⁷⁹ Appeal at 25; Behr Chronology at 2.

⁸⁰ Appeal at 26.

⁸¹ *Id.*

⁸² Behr Chronology at 2.

⁸³ Appeal at 26; Behr Chronology at 2.

⁸⁴ Behr Chronology at 2.

⁸⁵ June 3, 2016, General Advice letter.

⁸⁶ *Id.* at 1.

⁸⁷ *Id.* at 1-2.

⁸⁸ Unger email to the SDR Board, dated July 22, 2016.

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.⁸⁹

On July 6, 2016, Dr. Woodcock met with the review team one final time.⁹⁰ During the meeting, Dr. Woodcock "indicated to the review team that [she] had read their memoranda that had been updated to reflect the new [Western blot] data, and that [she] maintained [her] position that the application should receive accelerated approval based on dystrophin production."⁹¹ She discussed her rationale, which—based on her notes—appears to have tracked the rationale in her final decisional memorandum.⁹²

On July 8, 2016, in light of Dr. Unger's stated intention of filing an appeal with the Office of the Commissioner, Virginia Behr, CDER Ombudsman, began working with him and Dr. Woodcock to determine whether the institution of any formal appeals under CDER's SDR-SOPs was warranted.⁹³ Ms. Behr had determined that the procedure outlined in MAPP 4151.1,

⁸⁹ Unger email dated July 5, 2016.

⁹⁰ Appeal at 26; Behr Chronology at 3.

⁹¹ Woodcock's handwritten notes, dated July 6, 2016, at 1.

⁹² *Id.* at 2. Also of note, on July 7, 2016, Dr. Unger briefed you on his rationale for disagreeing with Dr. Woodcock's underlying scientific reasoning for granting accelerated approval for eteplirsen (Behr Chronology at 3).

⁹³ See "Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection" (SDR-SOPs Agreement).

“Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain” did not apply because the disagreement was between the Center Director and a subordinate two levels below her.⁹⁴ She also questioned the utility of using MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.”⁹⁵ She reasoned that “the CDER Director ha[d] already fully evaluated the issues and [was] one of the parties involved in the dispute” and that “utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”⁹⁶ She nonetheless consulted with both Drs. Unger and Woodcock, who both agreed to bypass the *Ad Hoc* panel process in favor of the process outlined in the SDR-SMG.⁹⁷ During his presentation to the SDR Board, Dr. Unger also indicated that he thinks referring the matter to an *Ad Hoc* panel would have been pointless because Dr. Woodcock had already made up her mind and a new process would not have changed the outcome.

On July 11, 2016, Dr. Woodcock provided a draft of her final decisional memorandum to the review team.⁹⁸ She received comments back from Dr. Unger; Dr. Jenkins, the Director of OND; and Dr. Ashutosh Rao, of the Office of Biotechnology Products, who was also on the review team.⁹⁹ The comments from Drs. Unger and Rao do not debate the action proposed in Dr. Woodcock’s draft decisional memorandum or its underlying scientific conclusions.¹⁰⁰ Instead, they focus on clarifying certain facts asserted in the memorandum, and Dr. Unger provided information regarding the clinical course of 11 patients enrolled in Study 201/202 to 240 weeks.¹⁰¹ Dr. Jenkins provided more detailed analysis on and critique of some of Dr. Woodcock’s findings and he expressed concern about her conclusions. However, he made no attempt in his written comments to dissuade her from her ultimate conclusion regarding accelerated approval.¹⁰² By email on the afternoon of July 13, Dr. Unger stated, “I’ve canvassed the Division, and we have no additional comments.”¹⁰³ Dr. Unger told the SDR Board that he and the review team understood that Dr. Woodcock had already made up her mind and that thus they did not see a point in criticizing Dr. Woodcock’s draft decisional memorandum.

Furthermore, the RTM told the SDR Board that some of the positions taken by Dr. Woodcock in the draft decisional memorandum were brand new to him but that he did not feel any feedback he could provide would receive due consideration by Dr. Woodcock. The RTM expressed concern that Dr. Woodcock’s analysis for “reasonably likely to predict clinical benefit” raised new issues and information that should have been presented at the beginning of the review and that had not been addressed by the review team or, perhaps more importantly, presented by the sponsor in support of the NDA. The RTM specifically discussed with the SDR Board the section of the finalized version of the memorandum addressing whether the data for eteplirsen is adequate to show a reasonable likelihood of predicting clinical benefit.¹⁰⁴ As an example of his concerns, the RTM pointed to section (B)(5) of the decisional memorandum, which details the findings in the

⁹⁴ *Id.* at 1. It is also clear from the record before the SDR Board that the supervisor between Drs. Unger and Woodcock, Dr. John Jenkins, agreed with Dr. Unger.

⁹⁵ *Id.*

⁹⁶ *Id.* at 2.

⁹⁷ *Id.*

⁹⁸ Behr Chronology at 3.

⁹⁹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); Jenkins email dated July 12, 2016; and emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰⁰ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰¹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰² Jenkins email dated July 12, 2016.

¹⁰³ Unger email dated July 13, 2016 and sent at 3:19 PM.

¹⁰⁴ Woodcock Decisional Memorandum at 5-10.

scientific literature regarding “the relationship of dystrophin expression to clinical status.”¹⁰⁵ The RTM indicated that he or she knows the scientific literature at issue very well and that he or she could have provided significant input into the evaluation of the literature and the underlying data and analysis. The RTM conveyed that he did not do so because he felt Dr. Woodcock had already made her decision.

On July 14, 2016, Dr. Woodcock finalized her decisional memorandum. She explained to the SDR Board that her conclusion regarding whether the increase in dystrophin production identified by Studies 202 and 301 was reasonably likely to predict clinical benefit was based on her own “medical/scientific judgment.” She emphasized that she has thirty years of experience at FDA and that she has far more experience in assessing this type of evidence for an “ultra-rare rare” disease than the review team. She thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case. Her stated goal for the decisional process was to move the review team toward what she viewed as a more reasonable approach. She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to “sure bet” drugs and that confirmatory trials are required for a reason. Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval. She also criticized OND for not issuing clear guidance on what constitutes a sufficient drug effect to be “reasonably likely to predict clinical benefit,” as she had suggested for an extended period of time. She also thought that the review team’s views on balancing the mean results of a clinical study with a targeted evaluation of responsive patients were misplaced, particularly in a DMD population, where additional genetic mutations or deficiencies could have a profound effect on the outcome.

In her presentation to the SDR Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

On July 16, 2016, Dr. Unger finalized his own decisional memorandum. In her own decisional memorandum, dated July 14, 2016, Dr. Woodcock indicated that she had read Dr. Unger’s decisional memorandum,¹⁰⁶ although she could not have done so given the timing of the two memoranda. She explained to the SDR Board that she did not feel she needed to see a finalized version of Dr. Unger’s decisional memorandum because she was already familiar with his views on the data and the decision. She also stated that there was nothing in Dr. Unger’s appeal, which is based largely on his finalized decisional memorandum, that would have changed her mind on her decision or the underlying rationale. She stated, “He is entitled to his own opinion.”

5. Dr. Unger’s SDR Appeal

In his appeal, Dr. Unger focuses his arguments almost exclusively on the substance of his scientific disagreement with Dr. Woodcock. Indeed, Dr. Unger makes clear in his appeal that he

¹⁰⁵ *Id.* at 7-10.

¹⁰⁶ *Id.* at 1.

seeks “a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit.”¹⁰⁷ Insofar as he explicitly addresses potential procedural issues under the review process contemplated by the SDR-SMG, he does so in two paragraphs toward the end of the appeal.¹⁰⁸ He first states that Dr. Woodcock’s “direct involvement with this drug, compared to other development programs, has been unprecedented.”¹⁰⁹ He states further that “[s]he also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.”¹¹⁰ After conceding that “[t]here is no question that there has been adequate time and place for the discussion of various views,” Dr. Unger notes that he found it unfortunate that “the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division’s final review memorandum or my review memorandum.”¹¹¹ As noted above, Dr. Unger indicates that Dr. Woodcock conveyed that she had “already ‘. . . reached a different conclusion . . .’ than the review team.”¹¹²

In his presentation to the SDR Board, Dr. Unger highlighted that Dr. Woodcock had never seen the charts on page 10 of his appeal. Those charts show: (1) a comparison of the *original* IHC results for baseline samples in the three patients whose biopsies were available at 180 weeks to the IHC results for those same samples when they were re-evaluated after 180 weeks and (2) a comparison of the IHC and the Western blot results at 180 weeks.¹¹³ Dr. Unger stated, however, that those charts were consistent with his earlier positions and would likely not affect Dr. Woodcock’s analysis or decision. In a follow-up email to the SDR Board, Dr. Unger also contended that Dr. Woodcock diverted from protocol when she finalized her decisional memorandum on July 14, 2016, two days before his.

In his appeal, Dr. Unger frames his scientific disagreement with Dr. Woodcock as follows: “The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit.”¹¹⁴ Nonetheless, Dr. Unger explains his disagreement with Dr. Woodcock through multiple challenges to the reliability of the underlying data and specific issues he has with her rationale or the evidentiary basis for such rationale. Of note, he makes the following scientific arguments:

- As noted above, Study 201 showed only “a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group...”;¹¹⁵
- Study 201/202 was fundamentally flawed in several respects:
 - “[T]he baseline biopsies were obtained from [external controls] . . . who could differ in unknown ways from the subjects in Study 201/202”;¹¹⁶
 - “[T]he Week 180 biopsies were obtained from different muscles than the baseline biopsies”;¹¹⁷ and

¹⁰⁷ Appeal at 26.

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.* at 10.

¹¹⁴ *Id.* at 3.

¹¹⁵ *Id.* at 9.

¹¹⁶ *Id.* at 5.

¹¹⁷ *Id.*

- “The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline...”¹¹⁸
- Although the available data generated by Study 301 were the product of an adequate and well-controlled study and showed a statistically significant increase of dystrophin, the drug effect (i.e., an increase from 0.22% to 0.32% of normal) is not reasonably likely to predict clinical benefit.¹¹⁹
 - “The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications”;¹²⁰
 - “Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that ‘...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.’ She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit”;¹²¹ and
 - “No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.”¹²²

He also makes several overarching policy and legal arguments that call into question the appropriateness of Dr. Woodcock’s decisional memorandum. His key arguments focus on the effects that Dr. Woodcock’s decision would have on the pathway for accelerated approval and the standard for “reasonably likely to predict clinical benefit.”¹²³ He also highlights the negative effects that accelerated approval would have on the patients themselves, including false hope, abandonment of other therapies, and a decline in drug development for DMD.¹²⁴ He further questions “the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic[] when the consequence of a sub-therapeutic dose is clinical deterioration and death.”¹²⁵ Finally he worries that approving eteplirsen based on the data submitted by the sponsor “would send the signal that political pressure and even intimidation—not science—guide[] FDA decisions.”¹²⁶

ANALYSIS

1. *Whether CDER followed its own processes.*

The first issue for the SDR Board to consider is whether CDER followed its own processes in addressing Dr. Unger’s scientific dispute. Dr. Unger does not contend that there were any issues with respect to how CDER chose to address and implement its own formal appeals process under the SDR-SOPs in this case. In his appeal, Dr. Unger points instead to four deviations from typical Center process: (1) Dr. Woodcock’s involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 7.

¹²⁰ *Id.* at 13.

¹²¹ *Id.* at 15.

¹²² *Id.*

¹²³ *Id.* at 21-22.

¹²⁴ *Id.*

¹²⁵ *Id.* at 23; *see also* Unger Review Memorandum at 4, 5.

¹²⁶ *Id.*

in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In its review of the administrative file and the surrounding circumstances, the SDR Board has also identified below other potential deviations from process at the Center level.

The agency-wide SDR-SMG directs the SDR Board to focus on the Center's SDR-SOPs in evaluating whether the Center followed its own processes in evaluating a scientific dispute. In this case, however, both Drs. Unger and Woodcock have agreed that the only applicable SDR-SOP, MAPP 4151.2, provides for a review by the Center Director in consultation with an *Ad Hoc* panel and that going through such a process at this stage would be futile. The SDR Board has determined that, absent the second aspect of that agreement regarding futility and the underlying unusual circumstance of this scientific dispute, there would be reason to refer the matter back to the Center for further review by an *Ad Hoc* panel.

The interplay between MAPP 4151.1 and 4151.2, the former of which provides for supervisory review of scientific disputes all the way to the Center Director, suggests that MAPP 4151.2 actually calls for additional review of a scientific dispute by the Center Director under certain circumstances even if she has already made a decision on the dispute. Although MAPP 4151.2 provides for bypassing review of the scientific dispute up the chain of command under MAPP 4151.1 if such exhaustion would impede the timely resolution of a serious public health issue, MAPP 4151.2 also emphasizes that it should not be used before other means of resolution have been attempted.¹²⁷ However, the key consideration for obtaining review by an *Ad Hoc* panel under MAPP 4151.2 is “whether the consequences of the decision in question are potentially serious enough to warrant [additional review],” not whether the resort to the process would be futile.¹²⁸ It appears that Dr. Woodcock has never made a determination regarding the seriousness of the decision in question, but it would be surprising if she determined that the dispute in this case did not meet the standard, as reflected in the statement she signed.¹²⁹

In this case, however, it is clear from the record before the SDR Board that Dr. Woodcock was so involved in the underlying scientific dispute—including direct and extensive personal review of the data and analyses offered in support of the NDA—that we agree with the conclusion in the agreements signed by Drs. Unger and Woodcock that “the CDER Director has already fully evaluated the issues.”¹³⁰ Indeed, she has already received advice from an advisory committee and had substantial conversations with her staff over an extended period of time with respect to the dispute in question. There is no reason to believe that receiving additional advice from an *Ad Hoc* panel would alter Dr. Woodcock's views of the scientific issues. As the agreement between her and Dr. Unger reflects, the process would be time-consuming and delay an important

¹²⁷ MAPP 4151.2 at 5. (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a [request for review under 4151.2] is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include . . . a written request to bypass these other mechanisms. . . .”).

¹²⁸ *Id.*

¹²⁹ SDR-SOPs Agreement at 2 (“The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.”).

¹³⁰ *Id.*

regulatory decision unnecessarily.¹³¹ Dr. Unger also told the SDR Board that he thought going through the *Ad Hoc* panel process would have been pointless for the aforementioned reasons.

The difficulty for the SDR Board is that the agency-wide SDR-SMG is predicated on some level of formal scientific dispute resolution within the Center, particularly a decision by the Center Director regarding the formalized scientific dispute.¹³² For that reason, the focus of the SDR-SMG with respect to the process followed is on whether the Center followed its own SDR-SOPs in resolving the scientific dispute.¹³³ Yet, the SDR-SMG also directs the Centers to adopt “[i]nformal methods” for resolving scientific disputes, “to create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” to use “good management practices for resolving conflict,” and “to enable as open and complete a discussion of the issues as possible at the working level of the organization.”¹³⁴ As a result, the SDR Board has determined that reviewing the processes used by a Center to resolve a scientific disagreement is appropriate under the SDR-SMG even when, as here, the initiator has not availed himself of the Center’s formal process for resolving scientific disputes and the Center Director has explicitly agreed to that approach.

Whether the Center followed its own processes for resolving a scientific disagreement cannot be viewed in a vacuum, however. Indeed, the SDR-SMG itself—at its most concise and in its clearest voice—states, “The goal of [the SDR Board’s] review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”¹³⁵ Particularly in the context of a scientific dispute that did not go through a formal SDR process at the Center but nonetheless received extensive review by the Center Director, focusing on deviations from process without any regard to whether they affected the initiator’s opportunity to present his views of the science (and to some extent whether those views and the evidence were considered) would seem to miss the point of that review. Accordingly, the SDR Board finds that it is more appropriate to address Dr. Unger’s arguments regarding the Center’s deviations from appropriate process under the second prong of its analysis: whether the Center provided Dr. Unger an adequate opportunity present his scientific concerns.

The SDR Board’s one caveat is that, as noted above, the SDR-SMG does appear to assume that there has been both at least some use of the formal dispute resolution within the Center and, accordingly, a *formal* substantive review of the initiator’s scientific concerns before reaching the Office of the Commissioner.¹³⁶ The limited scope of the SDR Board’s review under the SDR-SMG—i.e., an evaluation of the Center’s decision-making process—means that Dr. Unger will also not receive a substantive review of his scientific concerns under the SDR-SMG. In fact, at the conclusion of the SDR Board’s review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level. Particularly in light of

¹³¹ *Id.* (“[U]tilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”).

¹³² See SDR-SMG at 6 (requiring as a mandatory process for formal scientific dispute resolution a written opinion by the Center Director and stating that such a written opinion as a step in the process is a “central criterion for advancement to the agency-level appeals process.”).

¹³³ See, e.g., *id.* at 12 (requiring the SDR Board to “obtain the full administrative record of the Center’s processes for the dispute and review the Center’s published SOP(s)” and to “review that information to determine whether written Center processes were followed.”).

¹³⁴ *Id.* at 6.

¹³⁵ *Id.* at 12.

¹³⁶ See *id.* at 6 (referring to SOPs for resolution of Center-level scientific disputes without limiting them to procedural reviews and contemplating the Center SOPs as a continuation of the informal SDR process).

Dr. Unger's explicit request for scientific review of the matter within the Office of the Commissioner, therefore, the SDR Board recommends additional substantive review at this level, as is discussed below.

2. Whether CDER provided an adequate opportunity to Dr. Unger to present his scientific concerns.

In his appeal, Dr. Unger admits, "There is no question that there has been adequate time and place for the discussion of various views."¹³⁷ In so doing, he appears to concede away most of his arguments with respect to whether he had an adequate opportunity to present his scientific concerns, notwithstanding the procedural deviations he identifies. The SDR Board, however, has not taken Dr. Unger's concession at face value and has instead looked beyond it to evaluate the administrative file and the surrounding circumstances to identify additional procedural issues. We conclude nonetheless that Dr. Unger had an adequate opportunity to present his scientific concerns to Dr. Woodcock before she issued her decisional memorandum.

As noted above, Dr. Unger identified four deviations from Center's typical decision-making process for the eteplirsen NDA: (1) Dr. Woodcock's involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-1. In reviewing this matter, the SDR Board—which includes among its members Ombudsmen from other Centers that oversee reviews of medical products—also considered other departures from the typical processes used by Centers in reviewing applications for pre-market approval or clearance.¹³⁸

The SDR Board agrees with Dr. Unger that it was unusual for a Center Director to be so involved in the early stages of reviewing an NDA, but the consensus on the SDR Board was that Dr. Woodcock went several steps further than mere involvement and thereby departed from typical practice among the Centers. By her own admission, Dr. Woodcock had a direct hand in reviewing the data submitted in support of the NDA, even before the review team had written their draft review memoranda, and actively encouraged the review team—including Dr. Unger—to come around to her way of thinking in their own reviews. Specifically, she wanted the review team to agree with her that the limited increase in dystrophin production established by the data in Studies 201/202 was sufficient to show a reasonable likelihood of predicting clinical benefit. At several points during the decision-making process for what is clearly a critical scientific issue for the agency, Dr. Woodcock also provided a very limited amount of time for Dr. Unger and the review team to provide feedback on additional data or her own scientific conclusions—most notably when Sarepta submitted the data from Study 301 and when she provided two separate draft versions of her decisional memorandum to the review team.

Notwithstanding the foregoing procedural shortcomings, the SDR Board finds that Dr. Unger had an adequate opportunity to present his scientific views. Not only does he admit in his appeal that he had an opportunity, but the record before the SDR Board demonstrates that he did. He and the rest of the review team met with Dr. Woodcock on multiple occasions both before and after the AC meeting. Drs. Unger and Woodcock both told the SDR Board that those meetings involved substantive and detailed discussions of the data and science and the appropriate

¹³⁷ Appeal at 26.

¹³⁸ See SDR-SMG at 3 (defining the SDR Board to include Ombudsmen from all of the Centers).

conclusions to be drawn from them. Although Dr. Unger complains that Dr. Woodcock was involved in aspects of the NDA that went far beyond the norm for a Center Director at CDER, including her role in the AC meeting, and that she reached or finalized decisions before reviewing review or decisional memoranda, he does not maintain that those procedural deficiencies compromised his ability to present his views. In fact, his own final decisional memorandum—which Dr. Woodcock apparently saw in draft form before she finalized her own—discloses that he felt empowered to push back on both Dr. Woodcock’s scientific conclusions and their basis, despite the fact that he believed his efforts would be futile. Indeed, he conceded to the SDR Board that nothing in his decisional memorandum or appeal submission would have affected Dr. Woodcock’s decision on the scientific issue in question (including the charts that he created for the first time in preparing his appeal submission under the agency-wide SDR-SMG). He further conceded as much when he agreed not to pursue further review through the *Ad Hoc* panel process under CDER’s SDR-SOPs. In short, through his own perseverance, confidence in his own scientific expertise, and perhaps dint of personality, Dr. Unger ensured that he himself had an adequate opportunity to present his scientific views despite the procedural irregularities in the decision-making process within CDER.

The SDR Board nonetheless remains concerned about Dr. Woodcock’s extensive involvement in the review of the eteplirsen NDA, including her degree of participation at the AC meeting, and the limited timeframe she provided for feedback on the data from Study 301 and her own scientific conclusions on that data. We fear that those actions could have chilled scientific debate within CDER and reduced the level of participation by the review team during the final stages of the decision-making process. By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement. By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger. Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER’s review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval.

To complicate matters further, Dr. Woodcock subsequently circulated a draft decisional memorandum but provided only a limited amount of time for comments, even though the draft decisional memorandum was the first time some on the review team had apparently seen key elements for the basis of her decision on “reasonably likely to predict clinical benefit.” The response from the review team is telling. As noted above, only Drs. Jenkins and Unger and another reviewer outside of DNP provided comments. Except for Dr. Jenkins, no one made any effort to make substantive comments beyond tips on how to make factual clarifications or to supplement her analysis with additional data. It appears that, because the review team knew Dr. Woodcock’s views by then, they saw no point in providing any additional substantive review or meaningful feedback on any new issues raised by Dr. Woodcock’s memorandum. Indeed, Dr. Unger and the RTM conveyed as much to the SDR Board.

There is no doubt that a Center Director should have wide latitude in leading the direction of the Center in a manner consistent with her priorities and vision. The SDR Board also believes that Center Directors have a role to play not only with respect to the resolution of scientific disputes at issue in individual applications for pre-market-authorization by FDA, as evidenced by both the SDR-SMG and CDER’s own SDR-SOPs, but also with respect to the ultimate decision on

scientific issues that are not the subject of a dispute. It is also clear from Dr. Woodcock's presentation to the SDR Board that she firmly believes in the correctness of her scientific decision in this case and that her involvement in the review of the eteplirsen NDA was always motivated by the best of intentions. However, the SDR Board finds Dr. Woodcock's extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process.

Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had even completed their draft scientific reviews, Dr. Woodcock had told them—on May 4, 2016—that she intended to grant accelerated approval. This sort of top-down review does not, in the SDR Board's view, “create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” as reflected in the SDR-SMG's requirements for resolution of scientific disagreements by the Center.¹³⁹ By the time Dr. Woodcock issued her draft decisional memorandum on what she herself acknowledged was a difficult scientific issue of incredible magnitude for the agency—i.e., whether the evidence regarding dystrophin production was reasonably likely to predict clinical benefit—the review team had decided it was pointless to challenge her ultimate conclusion or its basis.¹⁴⁰ Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.

3. Whether the Center Director considered all relevant evidence bearing on the scientific question at issue.

The third issue for the SDR Board is whether CDER, including Dr. Woodcock, fully considered all relevant evidence in resolving the scientific dispute at issue, i.e., whether the evidence of eteplirsen's effect on dystrophin production is reasonably likely to predict clinical benefit. In this case, both Drs. Unger and Woodcock appear to agree that she *considered* all relevant evidence. As noted above, Dr. Unger does not believe that any additional data or evidence available to him could persuade Dr. Woodcock that she has reached the wrong scientific conclusion. For her part, Dr. Woodcock does not feel that she has disregarded any relevant evidence. Moreover, in her interview with the SDR Board, she demonstrated an awareness and command of all of the evidence weighing against the scientific decision she has made, including the arguments and analysis of the evidence presented in Dr. Unger's appeal.

Whether Dr. Woodcock has *addressed* all of the relevant evidence in her decisional memorandum is a more difficult question. In concluding that the minimal increase in dystrophin

¹³⁹ *Id.* at 6.

¹⁴⁰ In this regard, it is also worth noting again the language quoted above in the background section: “Each individual who contributes to the decision-making process” must “be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component” and that “[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made.” (MAPP 4151.8 at 2-3).

production seen in the data is reasonably likely to predict clinical benefit, Dr. Woodcock has provided a very limited rationale.

At the risk of oversimplification, Dr. Woodcock found, in essence, that the studies attempting to correlate levels of dystrophin with clinical benefit, as have been reported in the scientific literature, are unreliable in this context for variety of reasons, including: (1) the subjectivity of the clinical evaluation, (2) the difficulty in correlating IHC results with Western blot results, (3) the influence of anti-dystrophin antibodies, (4) the lack of information on dystrophin quality (as opposed to quantity) in the different studies, (5) deficiencies in Western blot techniques from earlier studies, and (6) the wide range of findings with respect to the correlation of dystrophin levels with clinical benefit.¹⁴¹ She concluded, therefore, 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,” and that the “biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.”¹⁴² She then attempted to bolster that conclusion with a theory regarding the effect of exon 52 deletion and her reanalysis of the intermediate clinical outcomes for a subset of subjects in Study 201/202.¹⁴³ She further explained to the SDR Board that she was exercising her “medical/scientific judgment” in reaching the scientific conclusion that she did.

It is easy for the SDR Board to understand why Dr. Unger’s appeal expressed such frustration with this explanation of Dr. Woodcock’s rationale. He states:

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients could benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.¹⁴⁴

Of course, *considering* the relevant evidence and *addressing* the relevant evidence in a manner satisfactory to Dr. Unger or the SDR Board are two different propositions. The SDR Board finds, based on the record before us, that Dr. Woodcock has considered all relevant evidence in reaching her scientific conclusion. Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger—both with respect to the scientific conclusion and the sufficiency of the underlying rationale.

4. Whether the dispute should be remanded to the Center Director.

Inasmuch as the SDR Board has concluded that Dr. Unger had an adequate opportunity to present his scientific concerns during the decision-making process at CDER and that Dr. Woodcock considered all relevant evidence in making her decision, the SDR Board does not recommend returning this matter to the Center Director for corrective action. We also believe that, for reasons discussed above, remanding this matter to the Center Director would be futile.

¹⁴¹ Woodcock Decisional Memorandum at 5-9.

¹⁴² *Id.* at 9.

¹⁴³ *Id.* at 10.

¹⁴⁴ Appeal at 20 (emphasis in original).

CONSIDERATIONS FROM THE ACTING CHIEF SCIENTIST

In my capacity as Acting Chief Scientist, I feel the responsibility to convey some comments regarding the underlying science for the decision being challenged by Dr. Unger in his appeal. I cannot begin to understand the depth of pain and suffering that patients with DMD and their families endure. As an experienced physician, I struggle to identify any other diseases associated with this degree of suffering, not only to patients but to their families. Nevertheless, my assessment is that the data presented by the sponsor to date are not adequate to support accelerated approval of eteplirsen

Studies in animals showing that eteplirsen leads to “exon 51 skipping” are an important first step in assessing whether eteplirsen might work for a subset of patients with DMD because skipping exon 51 is necessary for the production of dystrophin in these patients.¹⁴⁵ The next step is to assess whether eteplirsen actually leads to the production of dystrophin in patients with DMD and, if so, whether such an increase in dystrophin confers clinical benefit. Despite the promising animal studies demonstrating exon 51 skipping, both Drs. Woodcock and Unger, as well as the review team in CDER, agree that the amount of dystrophin produced in the clinical studies conducted at doses of up to 50mg/kg per week is very low. Animal data suggest that the doses studied in humans is too low; in animals, exon 51 skipping was detected in a nonlinear, dose-dependent manner (that is, higher doses led to significantly more exon 51 skipping). Specifically, with a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. These dose-dependent responses are important because it is wholly conceivable that higher doses would lead to a much greater amount of dystrophin production, which could be important for clinical benefit. Because the drug appears to be safe, the review team recommended evaluation of much higher doses of eteplirsen, of at least 200mg/kg per week. Approving a drug at a dose that does not show a meaningful increase in dystrophin (when the drug could theoretically achieve one at higher doses) is concerning.

As for accelerated approval, the regulatory standard at issue requires a sponsor to show that the drug under review leads to an effect on the surrogate endpoint (in this case, the production of dystrophin) and that the effect is reasonably likely to predict clinical benefit (in this case, improving, or slowing down decline in, muscle function). The term “reasonably likely to predict” acknowledges the potential for doubt in the outcome of interest. Indeed, nobody knows the minimum level of dystrophin that is likely to confer clinical benefit in patients with DMD. The critical scientific and regulatory issue at stake in CDER’s decision here is whether such minute amounts of dystrophin are reasonably likely to predict clinical benefit at the dosage of the drug subject to approval. In this case, both Drs. Woodcock and Unger have attempted to provide a rationale, based on scientific and professional judgment, for whether or not such small levels of dystrophin are reasonably likely to predict the clinical effect of interest. By any meaningful objective standard, however, the overall evidence derived from eteplirsen’s limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit. As pointed out in Dr. Unger’s appeal, “Study 201 did not show a treatment effect on its 1^o clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients.”¹⁴⁶

¹⁴⁵ Eteplirsen targets a subset of patients with DMD who are amenable to exon 51 skipping.

¹⁴⁶ Appeal at 16.

Some may argue that it would be reasonable to proceed with accelerated approval based on eteplirsen's safety profile, even where there are significant doubts about the drug's effectiveness. That argument does not take into account the risks of treatment with indwelling catheters to maintain vascular access in young patients, who would otherwise not need one and who often receive adjunct chronic corticosteroids, or, even more importantly, the detrimental impact on their quality of life.

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202¹⁴⁷—which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings. As determined by the review team, and as acknowledged by Dr. Woodcock, the article's scientific findings—with respect to the demonstrated effect of eteplirsen on both surrogate and clinical endpoints—do not withstand proper and objective analyses of the data. Sarepta's misleading communications led to unrealistic expectations and hope for DMD patients and their families. It is very disappointing that the findings did not hold up to careful review.

FDA must remain steadfast in its commitment to alleviating pain and suffering, approach the most challenging problems with absolute determination, and apply maximum flexibility to facilitate the development and availability of effective treatments. The agency's value centers on its ability to do all of the above while maintaining objectivity, even in the face of political pressure. FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard.

I acknowledge that there are currently no specific drugs available to treat patients with DMD and that issuance of a complete response letter would cast uncertainty on whether eteplirsen would continue to be developed, based on business and financial decisions that are external to FDA. However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions. Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.

I remain deep in my conviction that, through science and a flexible, sound regulatory approach, good therapies will emerge to provide meaningful clinical benefit to patients with DMD and other rare serious diseases.

THE SDR BOARD'S ADDITIONAL RECOMMENDATION

Although the SDR Board acknowledges that the scope of our review, as prescribed by the SDR-SMG, is limited to procedural questions, we nonetheless feel duty-bound to make one additional recommendation. As noted above, Dr. Unger seeks from the Office of the Commissioner a substantive, scientific review of Dr. Woodcock's decision to grant accelerated approval to

¹⁴⁷ See Mendell JR, et al. *Ann Neurol* 2013;74:637-47.

eteplirsen. The SDR-SMG presumes that an initiator such as Dr. Unger has received some substantive review of the scientific dispute at issue as part of a formal appeals process in the Center. Dr. Unger has never received any such formal review of his scientific arguments or the underlying evidence. To the extent he has ever received any substantive review of his scientific disagreement with Dr. Woodcock, Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor. Neither the SDR-SMG nor CDER's SDR-SOPs contemplate a scientific disagreement that arises between a Center Director and another manager in that same Center—partly because no one has ever anticipated the unique circumstance of this case. Especially given the SDR Board's concerns regarding the decision-making process at CDER, we think additional review within the Office of the Commissioner is appropriate.

The SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit. If you choose the latter, in light of the public and political pressure evident during the entire review process at CDER, as detailed in this recommendation, we believe that delegating this critical evaluation to a panel of experts would help ensure that the agency makes the most appropriate decision from the perspective of protecting patients and the public health, especially for DMD patients. Knowing as we do that you value cross-Center collaboration with respect to medical product development, we recommend that you include on the panel experts from other Centers devoted to the regulation of medical products. Doing so would not only help ensure diverse expertise on the panel but also provide insights on the effects that any proposed regulatory decision on eteplirsen might have on products regulated by those other Centers. We further recommend that you consider whether to include experts from other components within the Department of Health and Human Services and whether, consistent with applicable laws and the appropriate timeframe for a decision, you should also include outside experts on the panel.

SMG 9010.1

**FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM
DIRECTIVES**

GENERAL OR MULTIDISCIPLINE

DISPUTE RESOLUTION

SCIENTIFIC DISPUTE RESOLUTION AT FDA

Effective Date: 01/13/2009

1. Purpose
2. Background
3. Scope and Policy
4. Definitions
5. Responsibilities
6. Procedures
7. Effective Date
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1. PURPOSE

As part of the ongoing effort to improve the process of internal scientific dispute resolution, and to encourage open communication throughout the agency, this document describes how issues of scientific dispute are managed throughout FDA.

This document sets forth mandatory elements to be included in all scientific dispute resolution processes at the Centers, Office of Regulatory Affairs (ORA) and Office of the Commissioner (OC). In addition, the document provides recommendations for “best practice” activities related to scientific dispute resolution that are either ongoing in Centers, ORA, OC, other agencies or other outside organizations, or that have been suggested by focus groups with FDA employees.

This document also establishes an agency-wide appeals process for internal scientific disputes. Scientific disputes should be resolved whenever possible at the working level within the organization, and after full and frank discussion involving interested parties. When that is not possible, the process contained in this document provides all FDA staff an avenue to further pursue significant scientific disputes that they feel has not been adequately addressed within their Center, ORA or OC.

2. BACKGROUND

The September 2007 Values and Vision all hands broadcast communicated the organizational values that are important to the agency and set the course for the future with a three-part plan to develop leadership, improve processes and enhance resources for a science-led agency, and empower employees through effective communication. In addition, six Agency core values were unveiled: integrity, excellence, accountability, equity, diversity and transparency. The Commissioner, Dr. Andrew von Eschenbach, highlighted the importance to a scientific agency of encouraging and valuing presentation and discussion of differences of opinion. In that spirit, the process of addressing internal differing scientific opinions at FDA is being strengthened.

3. SCOPE AND POLICY

This Staff Manual Guide (SMG) is issued under the following guiding principles:

- FDA encourages the resolution of scientific disputes at the working level in the organization, starting with frontline employees and their immediate supervisors or team leaders.
- The agency's appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.

It is the Agency's policy that all staff should be aware of the paths available to them in case of issues of scientific dispute, that all staff, including initiators of disputes, are treated with openness and respect, and that the agency procedures should not be unnecessarily burdensome.

The FDA Scientific Dispute Resolution (SDR) program is intended to address serious scientific disputes concerning issues that could have a significant impact on public health. They are NOT intended to address issues related to personnel and work environment situations; these types of disputes already have processes in place for their resolution, as do other types of non-scientific disputes.

Every effort will be made to provide FDA staff with an opportunity to resolve scientific disputes internally. The agency-wide program for SDR has two components: agency requirements for the adoption of robust SDR processes at the Centers, ORA and OC (hereafter "Centers"), and an agency-wide process review. Through these processes, the agency will assure that all valid scientific disputes can and, if needed, will receive a full and fair hearing. (see Section Heading 5, sub heading E, for a description of the scope of the review that occurs at the Agency level).

Section 6.1 of this document details FDA's requirements for the minimum standards for scientific dispute resolution processes in the Centers. The Center SDR

requirements serve two purposes. First, robust Center processes foster the principle of resolution at the working levels within the organization. Second, the agency requires that a Center Director will provide a written decision on a case before the Commissioner will address it. These requirements ensure that disputes will be eligible for the agency's appeals process.

Section 6.2 of the document provides a collection of "best practice" SDR activities. The recommendations are not mandatory, but do reflect some of the best ideas for what thoughtful and effective Center SDR processes could include, and may be adopted by Centers as applicable to their own needs.

Section 6.3 of the document describes an appeals process for scientific disputes that are not resolved to the satisfaction of all involved at the Center level. The appeals process provides an avenue to internally resolve disputes by submitting a case for review to the Office of Accountability and Integrity and receiving a final decision from the Commissioner regarding the Centers' compliance with its procedures.

It is the responsibility of all those involved to ensure that all initiators of disputes are protected from any retaliation by their supervisors, peers, leadership and others, related to initiating or engaging in this process. This Staff Manual Guide does not supersede the fundamental protections pursuant to the Whistleblower Protection Act of 1989, the Federal Employee Anti-discrimination and Retaliation (No FEAR) Act of 2002 and all applicable federal laws, regulations and Executive Orders that afford protection under the law.

4. DEFINITIONS

- A. **Agency Scientific Dispute Process Review Board:** The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist. At the discretion of the Chair, additional members may be assigned to the Board on a case by case basis. The Board will assess whether Center processes were followed.
- B. **Initiator:** In the Agency dispute process, the initiator is the party that believes that a significant scientific issue has not been adequately addressed by Center dispute resolution processes. The initiator may be an individual, group, or organizational unit (division, office, etc.). Because scientific disputes at the agency might span more than one Center, initiators need not come from the same Center where the decision was made.
- C. **Scientific Dispute:** Disputes addressed through this process must be scientific in nature. Eligible disputes may, for example, involve the interpretation of science and decisions taken upon that interpretation. The following disputes are NOT

considered to be scientific disputes and would not be eligible for this process: personnel disputes such as EEO disputes, administrative disputes, labor and employment disputes, enforcement policy disputes and disputes related to the rule-making process.

5. RESPONSIBILITIES

- A. **Initiator of SDR process:** The initiator is responsible for submitting the initial documents needed for entry into the SDR appeals process to the Office of Accountability and Integrity (see Section 6.3.C.1 for requirements for complete submission). As soon as it is apparent that Center-level dispute resolution procedures have not resolved the dispute, the initiator should consider the potential public health impact and promptly file a formal SDR request, if appropriate. In addition, the initiator is responsible for fully cooperating with the formal SDR process; this participation may include presenting his or her case to the agency SDR committee(s), providing other documentation as necessary to the case review, and being interviewed by the committees.
- B. **Center and agency Ombudsman, or designated official from the Office of the Director:** Ombudsmen at the Centers and agency, or officials so designated, are responsible for being sufficiently familiar with the formal SDR process to effectively counsel potential initiators who approach their offices. At any point in the dispute process, these officials may be approached by the initiator, or any other persons involved in the dispute for consultation. Ombudsmen from the Centers and Agency will serve on the Agency Scientific Dispute Process Review Board. However, the Ombudsman of the involved Center will only participate in presenting the case and the Center's procedures to the Board, but will recuse him/her self from the Board's deliberations.
- C. **Center leadership:** Leaders at each Center are responsible for designing a new, or modifying an existing, SDR process for their organization, such that it incorporates all aspects as required by this SMG. Center leaders are also responsible for instituting SDR processes that reflect the guiding principles of openness and resolution of scientific disputes at the lowest organizational level possible. Finally, Center leaders are responsible for communicating the SDR process and training all Center staff on the informal and formal procedures available to resolve scientific dispute internally.
- D. **Center Directors:** For each scientific issue under dispute, Center Directors are responsible for ensuring that the SDR process in their organization is documented, communicated, implemented, and conforms to the standards required by the agency (see 21 CFR 10.70 and Section 6.1). This responsibility includes maintaining and providing a complete administrative record of the SDR process that was followed for each dispute. They are also responsible for rendering written decisions on disputes that have advanced to them through the scientific dispute resolution processes in their individual organizations. Center Directors are

also responsible for cooperating with the agency's appeals process through interviews, information requests, and presentations to the agency SDR committees, as necessary. Finally, the Center Director is responsible for working closely with the agency SDR committee, the Chief Scientist and the Commissioner throughout an appeal, and carrying out any corrective actions that the Commissioner requires.

- E. Agency Scientific Dispute Process Review Board:** Responsible for conducting full and fair evaluations of the disputes to assess whether the Center's processes were followed, whether the Center considered all relevant evidence bearing on the scientific question at issue, and whether the initiator was provided an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.

Specific responsibilities of the Board include the following:

- Collecting all information needed to fairly and objectively review a case
- Consulting all expert opinions that are relevant to the review of each case
- Documenting the findings and rationale behind any recommendations it makes
- Communicating the findings and recommendations to the Commissioner

The Board is also responsible for notifying the Center Director when a decision at their Center is being appealed. In every dispute, members of the Board from Center(s) where disputes arise will recuse themselves from the dispute review process.

- F. Chief Scientist (CS):** The Chief Scientist will chair the Agency Scientific Dispute Process Review Board. The CS will make recommendations to the Commissioner about whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or her concerns; that all relevant evidence bearing on the scientific question at issue has been considered; and, whether the dispute should be remanded to the Center Director.
- G. FDA Commissioner:** When Center decisions are appealed, the FDA Commissioner will be responsible for rendering a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns; whether all relevant evidence bearing on the scientific question at issue has been considered; and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

6. PROCEDURES

6.1 REQUIREMENTS FOR SDR PROCESSES AT THE CENTERS

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization. If informal attempts fail, requirements for the formal procedures for resolving disagreements at each Center are described below.

A. Requirements for Inclusion in the Formal Scientific Dispute Resolution Process at Each Center

The following requirements should be considered mandatory process inclusions, and must be incorporated into Center activities within Fiscal Year 2008:

1. Required elements of each Center's Standard Operating Procedure (SOP)
 - a. Each Center is required to have an SDR SOP
 - b. If a dispute is not resolved before reaching a Center Director, the Director must render a written opinion on the matter, as this step is a central criterion for advancement to the agency-level appeals process.
 - c. While the scientific dispute resolution process is pending, work on the application and a final regulatory decision will continue unless the Center Director decides that:
 - (1) The appeal raises substantial questions involving a significant risk to the public health, and
 - (2) Postponing the decision would not result in a negative impact on the public health.

Further, center personnel are not expected to postpone regulatory decisions on INDs, IDEs, Food Contact Substance Notices, etc.

- d. Timeframe for rendering a written opinion must be included, and should be developed by each Center consistent with regulatory/statutory timeframes.
 - e. Each SOP must make reference to the agency-level process as the appeals process for a dispute, should the Center-level dispute resolution process be exhausted.
 - f. Timeframes for elevating a dispute to the agency scientific dispute appeals process must be included in the Center SOP.
 - g. Each SOP should include a process by which disputes of sufficient immediacy and scale of impact to public health are able to 'opt-up' to the Center Director in order that he or she can make a decision on the matter within a condensed timeframe.
 - h. SOPs must include certain key messages for SDR
 - (1) SOPs will encourage dispute resolution at the lowest organizational level possible.
 - (2) SOPs will encourage open communication throughout the organization.
 - (3) SOPs will clearly state that initiators will be protected from any repercussion or retaliation by supervisors, Center leadership, and peers.
 - i. Each SOP will make clear the roles and responsibilities of Center staff in the SDR process, including that of the Ombudsman, where one exists.
2. Required communication in each Center's SDR process
- a. Center leadership is responsible for developing and disseminating clear written procedures for internal scientific dispute processes, including the timeline for rendering a written opinion. Center leadership is also responsible for communicating SDR responsibilities to all levels of staff on an annual basis.
 - b. FDA's Administrative Practices and Procedures Regulations provides that all FDA employees responsible for handling a matter are also responsible for insuring the completeness of the administrative file (see 21 CFR 10.70).

- c. In addition to documentation required by 21 CFR 10.70, decisions related to the formal SDR process and their supporting rationale will be documented.
- d. At all Centers, decisions related to the formal SDR process and their supporting rationale will be communicated to appropriate parties.

6.2 RECOMMENDATIONS FOR SDR PROCESSES AT THE CENTERS

The following recommendations are offered as FDA's perspective on "best practice" SDR activities. While these recommendations are not considered mandatory, they do reflect some of the best ideas for what a thoughtful and effective Center SDR process could include, and can be adopted by Centers as applicable to their own needs.

A. Best Practices for Formal Scientific Dispute Resolution Processes at the Centers

1. Recommended communication in each Center's SDR process
 - a. Centers could employ various mechanisms to disseminate their SOPs
 - (1) Mechanisms for dissemination could include, but are not limited to, one or more of the following: e-mail, orientation for new staff, workshops, hard copy distribution, online training programs, and an interactive SDR website, interactive SDR slide presentation.
 - (2) Centers may decide to regularly reinforce the importance of SDR via Center retreats or other annualized training programs
 - b. Center SOPs should require that only written documentation of a dispute will trigger a formal dispute resolution process. This step would ensure that the necessary historical record of the dispute is available should it advance to the agency-level appeals process.
 - c. Centers may require each side of the scientific issue under dispute to present their case in writing to enable transparent review at successive steps of the process. It is also considered best practice to document all decisions made at successive levels in the dispute process.

Additionally, in-person meetings with the initiator of the dispute to communicate final decision(s) and rationale may be adopted by Centers as they see fit.
2. Recommended role of the Center Ombudsman, or designated official in the Office of the Director, in the Center's SDR process.

The Center Ombudsman could informally communicate with initiators throughout the SDR process to increase the initiators' comfort with it.

3. Training and mentorship as tools to encourage open communication and the resolution of scientific disputes
 - a. Because supervisors and scientists are often the first level where scientific disputes arise, they may be trained on good management practices, including how to resolve disputes.
 - (1) Centers may institute training programs for all staff on the SDR process and good dispute resolution practices in general.
 - (2) Centers may implement procedures to evaluate supervisors on their management skills and ability to resolve scientific disputes.
 - (3) Centers may enable a "feedback loop" through Center Ombudsmen to counsel individuals (e.g., supervisors or working-level staff) who are frequently involved in formal scientific disputes.
 - b. Mentorship and training programs to encourage open communication
 - (1) Scientists may be paired with non-supervisory mentors.
 - (2) Institute training to produce team norms, process of managing conflict in teams, team charters, etc. for review teams and other groups.
4. Monitoring use of the SDR process

Centers may include questions on annual staff surveys to gauge awareness of and satisfaction with SDR process.
5. Possible formal avenues for scientific dispute resolution apart from chain-of-command mechanisms
 - a. Utilize external experts to seek objective perspective, additional scientific expertise, and practical knowledge. Examples of these are experts from other Centers, ORA and OC, other agencies, and SGEs, who can be used for written consultation.
 - b. Make several avenues available to address scientific issues: regulatory briefings, advisory committees, internal discussions with Center Directors, standing subject matter committees, and multi-disciplinary teams.

B. Best Practices for Informal Scientific Dispute and Communication

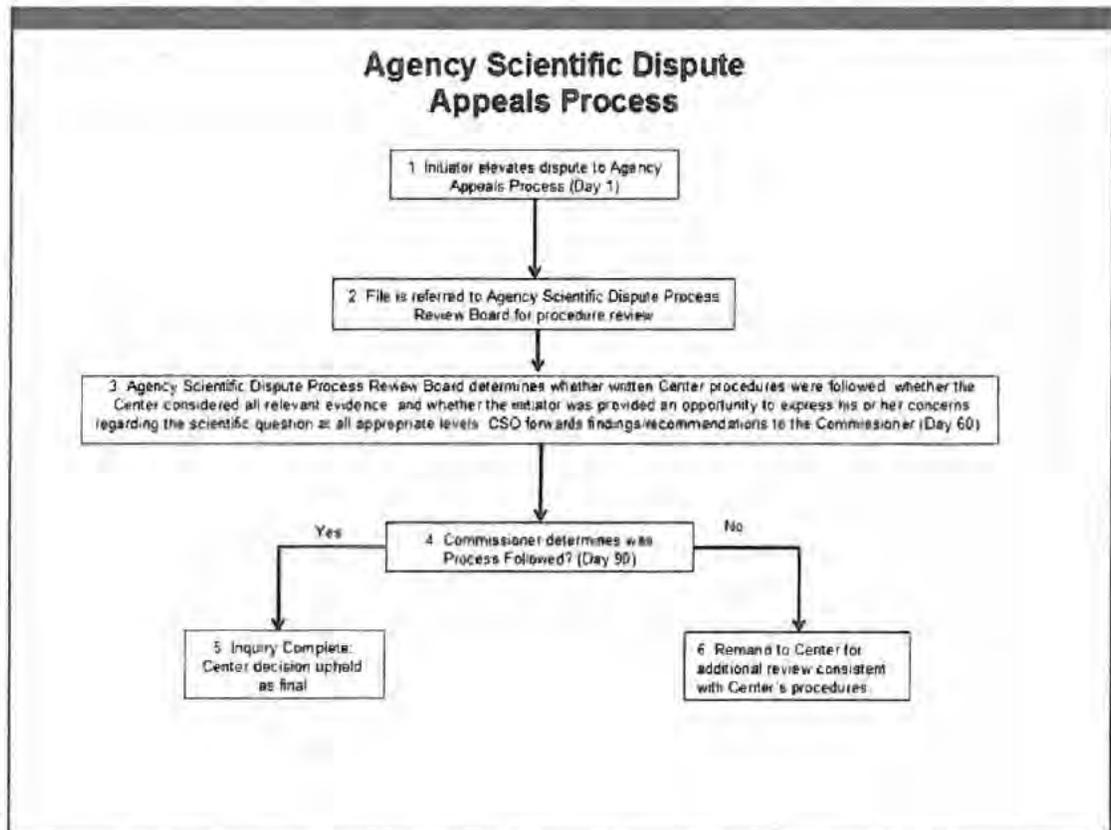
Every effort should be made to informally resolve differences in opinion on scientific matters. There are a variety of methods that Centers and other organizations already employ to foster informal dispute resolution, and still more that were suggested by internal focus groups.

A non-exhaustive list of informal resolution mechanisms includes the following:

1. Institute informal peer review and / or round table discussions. One method could be to institute formalized weekly meetings to informally discuss “hot topics,” or issues of potential dispute.
2. Use Center Ombudsman (if applicable) for informal perspective and to help filter personnel-related issues.
3. Increase two-way communication within the review process. For example, Centers could choose to have employees meet regularly with their supervisors as a review team to discuss on-going reviews, substantive problems and their recommendations.

6.3 DESCRIPTION OF THE AGENCY’S APPEALS PROCESS FOR SCIENTIFIC DISPUTES

If an initiator is not satisfied after engaging in the scientific dispute resolution process at the Center, this appeals process provides an additional avenue to resolve disputes internally. All scientific disputes under appeal will be reviewed by the Agency Scientific Dispute Process Preview Board, and the Commissioner will make a final decision about the issue under dispute.



A. Description of appeals process for scientific disputes

1. Elevation of disputes to the appeals process marks entry of internal scientific disputes into the formalized agency SDR appeals process. Disputes can advance from the individual Center-level SDR processes into the appeals process if the initiator feels that the dispute has not adequately been addressed / resolved at that level. The initiator must elevate the scientific dispute issue to the agency appeals process within 10 days of receiving the written opinion rendered by the Center.

At this step, the initiator must submit the case, in writing, to the Office of Accountability and Integrity (OAI). Receipt of case by OAI will be mark the first day of the agency scientific dispute appeals process. The submission will include:

- Description of how the initiator's position differs from Center's perspective
- Assessment of possible impact to public health should initiator's position not be adopted

- Detailed description of the history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process
 - Action, decision or remedy sought
2. The Agency Scientific Dispute Process Review Board will review the initiator's file, and obtain any other information necessary, to evaluate whether it meets the criteria for review. Other necessary information may include written documentation from the Center. They will assess the information and conclude whether the case meets the following criteria:
- At a minimum, the dispute must be scientific in nature. The Board will not evaluate disputes that are not based on science.
 - The Center Director must have rendered a decision on the scientific issue under dispute.

The Board will notify the Center Director that a scientific dispute has been submitted for appeal.

3. The Board will gather all necessary additional information that will enable a fully-informed recommendation on the case. The Board will obtain the full administrative record of the Center's processes for the dispute and review the Center's published SOP(s). As needed, the Board will conduct interviews with all relevant parties in the dispute, which may include the initiator, team leader, Center Director, and others. They will review the information to determine whether written Center processes were followed

The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director. The Board will document findings and recommendations and the Chief Scientist will present his or her recommendations to the Commissioner. Representatives of the involved Center will not participate in this review.

The Board should complete its review by the sixtieth (60) calendar day in the agency SDR appeals process.

4. If the Agency Scientific Dispute Process Review Board determines that the Center's processes and procedures were followed appropriately, that the Center fully considered all relevant evidence and the initiator was provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Center's decision will be

upheld as final and a written recommendation will be distributed to all internal parties involved in the dispute. The Board findings will be forwarded to the Commissioner and the agency SDR process will be concluded.

5. If the Agency Scientific Dispute Process Review Board finds that the Center's processes and procedures were not followed appropriately, that the Center did not fully consider all relevant evidence and/or the initiator was not provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Chief Scientist will provide a written recommendation to the Commissioner that the case be returned to the Center for additional review consistent with the Center's procedures. This memo will consist of the Board's rationale for the recommendation, all minority opinions from panelists, and a proposed statement to be used to communicate the Commissioner's decision.
6. The Commissioner will review the Board's recommendation and render a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns, and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

The Commissioner will communicate this decision, and a short rationale for the decision, in writing to each side of the dispute.

The final decision will be rendered by the Commissioner, by the ninetieth (90) calendar day of the agency SDR appeals process.

B. Anticipated timing of the scientific dispute resolution appeals process

1. From the time that the initiator submits a dispute to the Office of Accountability and Integrity for review, the SDR appeals process will be completed within 90 calendar days.
2. At the discretion of the Commissioner, the process may be accelerated because of statutory or regulatory timelines or urgency of agency decision.

C. Documentation requirements throughout the SDR appeals process

1. Documentation required for entry to the process

The initiator's written case must include the following elements:

- (1) Description of how the initiator's position differs from Center's perspective

- (2) Assessment of possible impact to public health should initiator's position not be adopted
- (3) Detailed description of history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process
- (4) Action, decision or remedy sought

7. EFFECTIVE DATE

The effective date of this guide is January 13, 2009.

8. Document History -- SMG 9010.1, Scientific Dispute Resolution at FDA

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	01/12/2009	N/a	OC/OP/OAI , HF-22	Susan C. Winckler, FDA Chief of Staff

From: [Behr, Virginia L](#)
To: [Woodcock, Janet](#)
Subject: RE: Appeal
Date: Monday, July 25, 2016 11:30:27 AM

I didn't think his memo did, but I mentioned it to them anyway.

From: Woodcock, Janet
Sent: Monday, July 25, 2016 10:55 AM
To: Behr, Virginia L
Subject: RE: Appeal

Yes, if you think Ellis's memo leaves the impression that these Offices are part of the appeal. jw

From: Behr, Virginia L
Sent: Monday, July 25, 2016 8:30 AM
To: Woodcock, Janet
Subject: RE: Appeal

Janet,

Thanks for letting me know. Right now, I don't have a proactive role on the Agency Scientific Process Review Board other than presenting to the Board this morning (our dispute resolution processes and a brief regulatory history) and responding to their requests for documents. However, I can suggest to the Board that they discuss the issue with leadership in OB, OCP, and OBP. Do you advise that I do so?

Virginia

From: Woodcock, Janet
Sent: Sunday, July 24, 2016 10:07 AM
To: Behr, Virginia L
Subject: Appeal

Virginia I ran into Lisa LaVange Friday at med policy council. She told me she looked at Ellis's memo and she wanted to be clear that the Office of Biostats feels dystrophin production was statistically verified and has no opinion on the reasonably likely issue. Also I was talking to Steve Kozlowski to make sure he was aware of the appeal and he stated that his Office has no role in the reasonably likely issue. I don't know about Clin Pharm. But you might want to ascertain the position of these offices to make sure there is no confusion. Lisa was a bit exercised. Jw.

From: [Walsh, Sandy](#)
To: [Woodcock, Janet](#)
Subject: RE: Revisions to eteplirsen communications QA and press release
Date: Monday, July 25, 2016 11:16:13 AM
Attachments: [eteplirsen PR draft OCC OMA Ocomm 072516 doc.doc](#)
[image019.png](#)
[image001.png](#)

Thanks, do you have any comments on the press release?

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669 | Cell: 240-328-7088
sandy.walsh@fda.hhs.gov



From: Woodcock, Janet
Sent: Monday, July 25, 2016 11:11 AM
To: Walsh, Sandy
Subject: RE: Revisions to eteplirsen communications QA and press release

Here it is. jw

From: Walsh, Sandy
Sent: Monday, July 25, 2016 11:09 AM
To: Woodcock, Janet
Subject: RE: Revisions to eteplirsen communications QA and press release

This attachment is the pain management stuff. Who does that need to go back to?

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669 / Cell: 240-328-7088
sandy.walsh@fda.hhs.gov



From: Woodcock, Janet
Sent: Monday, July 25, 2016 11:08 AM
To: Walsh, Sandy
Subject: RE: Revisions to eteplirsen communications QA and press release

Here are my edits. Have some comments inside the text. jw

From: Walsh, Sandy
Sent: Monday, July 25, 2016 10:20 AM
To: Woodcock, Janet
Cc: Bolek, Michelle; Shreeve, Chris; Ligon, Sharnell (CDER)

Subject: Revisions to eteplirsen communications QA and press release

Hi Dr. Woodcock,

I know you've reviewed the eteplirsen communications already. We are continuing to update the responsive QA and the press release so that we can be ready in the event of an approval action. I've made additional edits based on the most recent version of the drug labeling and on your decisional memo. I think it will be important to reflect your thoughts from the memo in our communications materials.

We added a few new "hard" questions at the end of the QA that we think we will be asked. I attempted to draft responses but would appreciate getting your views on what to say. Please take a look at the most recent versions. If you'd prefer, I can schedule some time with you to come over and walk through the documents.

Thanks again. Hopefully we'll be able to finalize these soon.

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669 / Cell: 240-328-7088
sandy_walsh@fda.hhs.gov



FDA NEWS RELEASE

For Immediate Release: August xx, 2016

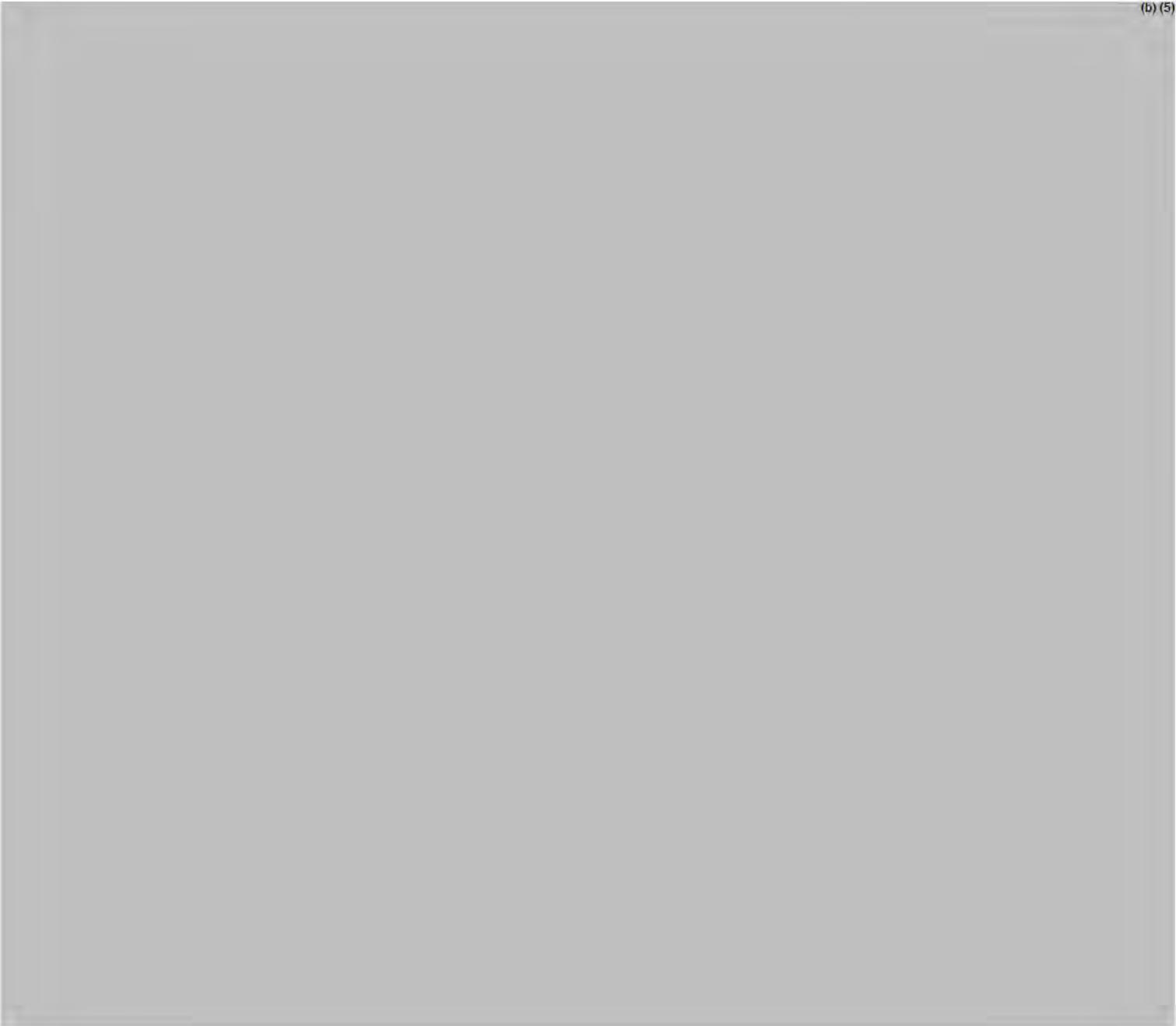
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

(b) (5)



(b) (5)



From: [Walsh, Sandy](#)
To: [Woodcock, Janet](#)
Subject: RE: Revisions to eteplirsen communications QA and press release
Date: Monday, July 25, 2016 12:22:49 PM
Attachments: [image019.png](#)
[image001.png](#)

Are you thinking of further clarifying the .93% description in section 14 of the labeling? Just curious.

Sandy Walsh

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669 / Cell: 240-328-7088
sandy.walsh@fda.hhs.gov



From: Woodcock, Janet
Sent: Monday, July 25, 2016 11:20 AM
To: Walsh, Sandy
Subject: RE: Revisions to eteplirsen communications QA and press release

No I thought it was fine. The nuance in the other document is that the Office of new drugs believes there is substantial evidence of increasing dystrophin production, but they just don't think it is enough dystrophin. Using the mean value (0.93% of normal) I find a bit misleading. Some of the boys did not respond at all, both in the first set and the second. Since their mutations are different, this makes some sense, in some way, the target of the drug is different in each boy, except maybe the twins. A better way to put it would be between 0.25% (the lower limit of detection) and 2.5% of normal, depending on the boy. jw

From: Walsh, Sandy
Sent: Monday, July 25, 2016 11:16 AM
To: Woodcock, Janet
Subject: RE: Revisions to eteplirsen communications QA and press release

Thanks, do you have any comments on the press release?

Sandy Walsh

Press Officer

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From: Walsh, Sandy
Sent: Monday, July 25, 2016 10:20 AM
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Cc: Bolek, Michelle; Shreeve, Chris; Ligon, Sharnell (CDER)
Subject: Revisions to eteplirsen communications QA and press release

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We added a few new "hard" questions at the end of the QA that we think we will be asked. I attempted to draft responses but would appreciate getting your views on what to say. Please take a look at the most recent versions. If you'd prefer, I can schedule some time with you to come over and walk through the documents.

Thanks again. Hopefully we'll be able to finalize these soon.

Sandy Walsh

Press Officer

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-4669 / Cell: 240-328-7088

sandy.walsh@fda.hhs.gov



From: [Moscicki, Richard](#)
To: [Woodcock, Janet](#)
Subject: Sareptafinal.docx
Date: Thursday, July 21, 2016 2:49:17 PM
Attachments: [Sareptafinal.docx](#)

As I said this morning, I think this is very good but I thought I would also pass along some minor thoughts. Rich.

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER),
Food and Drug Administration

SUMMARY



13 pages of draft language have been withheld as b(5) immediately following this page

From: [Behr, Virginia L](#)
To: [Woodcock, Janet](#)
Subject: Fw: Appeal - NDA 206488 Eteplirsen
Date: Tuesday, July 19, 2016 3:32:41 PM
Attachments: [Eteplirsen Appeal Unger 7-18-16.pdf](#)

Got the okay to share with you.

Virginia

Sent from my BlackBerry 10 smartphone.

From: Unger, Ellis
Sent: Monday, July 18, 2016 7:04 PM
To: Warren, Matthew
Cc: Behr, Virginia L; Lauritsen, Kristina
Subject: Appeal - NDA 206488 Eteplirsen

All,

Here is the appeal. Please let me know if I should place it in DARRTS.

Ellis

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Evaluation and Research
US FDA

Agency Scientific Dispute – Appeal

Date: July 18, 2016

To: **G. Matthew Warren**
Director
Office of Scientific Integrity, FDA

From: **Ellis F. Unger, M.D. (initiator)**
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Re: **NDA #** 206488
Drug: eteplirsen (Exondys 51)
Applicant: Sarepta Therapeutics
Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

1. Background

The Office of New Drugs within the Center for Drug Evaluation and Research (CDER) oversees regulation of new drugs, and is responsible for making regulatory decisions for approval/non-approval of new molecular entities. Within the Office of New Drugs, there are 6 sub-offices, including the Office of Drug Evaluation-I. The Office of Drug Evaluation-I oversees the Division of Neurology Products, which regulates drugs for the central and peripheral nervous systems, as well as drugs for muscular disorders. Typically, a new drug application (NDA) for a new molecular entity for a neurology indication is reviewed by the Division of Neurology Products in concert with review staff from other offices in CDER.¹ The regulatory decision is typically rendered by Office of Drug Evaluation-I, i.e., the signatory authority.

NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a *complete response* action. This view was shared by the Office of Biometrics, which performed the statistical review, as well as the Office of Clinical Pharmacology, which performed the pharmacology review. Dr. John Jenkins, Director, Office of New Drugs, also supports a *complete response* action for this NDA (verbal communication).

This memo is meant to explain the salient arguments around the scientific disagreement here; additional details are available in my memo recommending a complete response and Dr. Woodcock's memo recommending approval, and the reader is referred to those memoranda.

Disease Background:

¹ Reviews are typically provided by Office of New Drug Quality Assessment, Division of Medication Error Prevention and Analysis, Office of Biometrics, Office of Scientific Investigations, and others.

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys.

Dystrophin protein is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation. Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, there is loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Steroids are currently the cornerstone of management, widely believed to delay loss of ambulation and respiratory decline by several years.

Drug Background:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, by restoring of the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.

Drug Development Background:

Three studies are germane to the issues here. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study (see below).

The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.

2. Description of How My Position Differs from the Center’s Perspective

Dr. Janet Woodcock, Director, CDER, disagrees with some of the findings of the review team, and has reached the conclusion that the NDA should be approved. She finds that the data meet the standard for accelerated approval under 21 CFR 314. 510, based on the change in a surrogate endpoint of dystrophin protein production – a change she concludes is reasonably likely to predict clinical benefit. The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit. The decision of *approval vs. complete response* hinges on this question.

a. Clinical/Statistical Efficacy

Accelerated Approval:

Dr. Woodcock has reached the conclusion that eteplirsen should receive accelerated approval based on a small effect on the surrogate endpoint of dystrophin production.

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept “...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied. There is no disagreement.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 2) whether the effect demonstrated meets the test of being “reasonably likely” to predict clinical benefit. Importantly, there is no regulatory definition of “reasonably likely.”

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. There is no disagreement here.

The second part of factor 3 is whether an effect has been demonstrated; the legal standard is ‘substantial evidence’ based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05, but in some situations FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness.² Dr. Woodcock believes that “...there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.” I agree that there is evidence from a single adequate and well controlled trial, Study 301, that eteplirsen induces dystrophin production in muscle cells, but do not agree that there is reliable quantitative evidence from the other trial, Study 201/202.

The third part of factor 3, the conclusion that the demonstrated effect is “reasonably likely” to predict clinical benefit, is where there is disagreement.

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

Dr. Woodcock cites 3 lines of evidence pertinent to the conclusion that eteplirsen increases dystrophin production:

1. Production of an appropriate mRNA transcript
2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot
3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

1. Production of an appropriate mRNA transcript

I agree that the applicant has shown expression of mRNA following treatment with eteplirsen. As noted by Dr. Woodcock, this finding establishes proof of concept, but does not by itself mean that there is increased dystrophin production.

2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot

Western blot is a standard laboratory technique used to quantify proteins in body tissues. In Sarepta’s development program, Western blot was used to assess dystrophin protein levels in skeletal muscle in Study 201, in Study 202 (again, these were Study 201 patients who were maintained on treatment), and finally in Study 301.

a. Study 201:

The original Western blot analyses from Study 201 were intended to show that dystrophin levels were greater in eteplirsen-treated patients than in patients in the placebo group, and analyses were planned to compare the effects of the lower vs. higher eteplirsen doses on dystrophin production. The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.

b. Study 202:

² See: “Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;” May, 1998.

With FDA's assistance, the applicant improved the assays and performed repeat biopsies on 11 of 12 patients of the Study 201/202 patients at Week 180. These were to be compared to stored baseline (pre-treatment) samples; however, evaluable tissue was available for only 3 of the 11 patients. The baseline samples are germane to the determination of the treatment effect because the Week 180 biopsies showed only a small quantity of dystrophin (mean = 0.93% of normal). Thus, for the purpose of computing the *change* in dystrophin resulting from eteplirsen treatment, even small differences in the baseline level are critical.

As noted by Dr. Woodcock, the review team and I had concerns about these controls, leading us to conclude that Study 201/202 was not adequate and well controlled:

1. The goal was to assess the change in dystrophin with treatment, i.e., pre-treatment vs. post-treatment, but most of the baseline biopsies were obtained from subjects external to Study 201/202, who could differ in unknown ways from subjects in Study 201/202.
2. For all patients, the Week 180 biopsies were obtained from different muscles than the baseline biopsies, and studies of both normal human muscle and non-clinical DMD models have shown that dystrophin levels vary among muscles.
3. The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline, accordingly.

Dr. Woodcock believes that "...these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion." She notes that the external control patients were similar in age and mutation site to the patients in Study 201/202. She found little difference between dystrophin results across different muscle groups, and little difference based on storage time, leading her to believe that these factors "...did not result in large differences in the findings."

Although I agree that these factors are not likely to lead to large differences, even small differences would affect the calculation of the *change* in dystrophin at Week 180, because the Week 180 values were quite small (mean only 0.93% of normal). At issue is how much of the dystrophin detected at Week 180 was newly produced, vs present at baseline. For example, a difference in the baseline level of only 0.30%, although minute, is substantial compared to 0.93%.

Dr. Woodcock notes that at Week 180, 2 subjects had dystrophin levels between 2 and 3%, 2 had a level between 1 and 2%, and 2 had a level of ~1%. She notes that 2 of these subjects had both baseline and Week 180 samples, and there were clear increases in dystrophin in these 2 patients. Of note, Dr. Woodcock points out that although some subjects had Week 180 dystrophin levels similar to the baseline (i.e., close to zero), she would expect this because she would not predict that all individuals would respond to a drug intervention.

She explains that 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.”

In the end, taking Dr. Woodcock’s arguments into consideration, my view is that the data from Study 202 are *suggestive* of an increase in dystrophin in response to eteplirsen, but the study was not adequate and well controlled. If we accept that there *is* a difference, Study 202 does not reliably speak to the *amount* of dystrophin produced by eteplirsen, given the concerns above. There is only certainty that the largest *possible* amount was 0.93% of normal (on average), and <3% in any individual (if we assume that the quantity was zero at baseline).

Below I will present another concern that leads me to question the veracity of the Western blot data from the Week 180 biopsies from Study 202, based on an issue that Dr. Woodcock did not address in her memo.

c) Study 301:

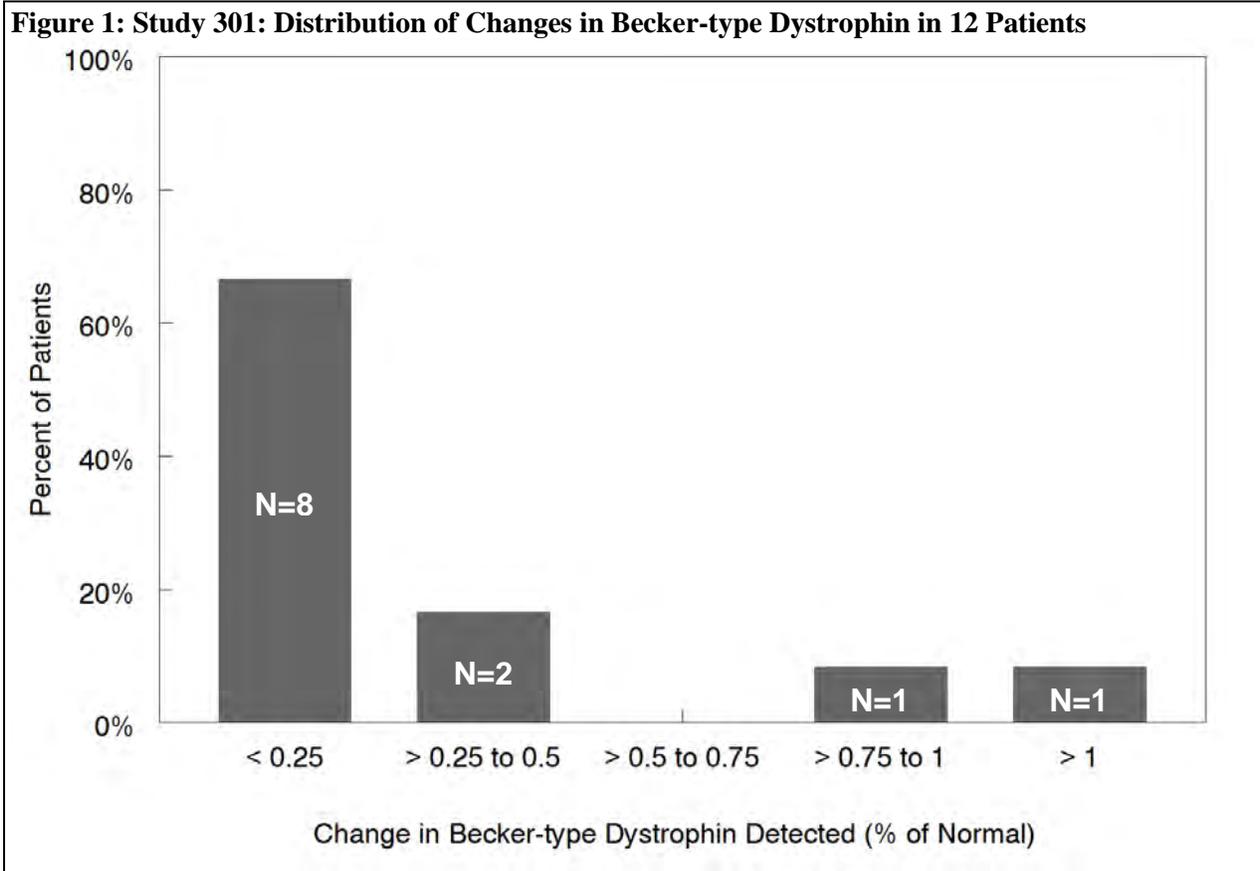
With the May 26, 2016 goal date approaching, OND and CDER could not reach agreement on the regulatory action for this NDA. In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301, PROMOVI). These samples were originally planned to be analyzed at the end of the study; however, we requested an interim analyses of a subset of samples. Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples obtained at baseline (prior to treatment) were compared to those obtained at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

The data are shown in Table 1 and the distribution of these changes is shown graphically in Figure 1. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change greater than 1%. The applicant used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.24	1.33
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08		
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	1.57	1.33
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17		
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.12	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12		
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.47	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31		
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.09	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09		
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34		
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25	13	Baseline	fail	0.34	0.21	0.03
		pass	0.17					pass	0.21		
	Week 48	fail	0.22	0.42			Week 48	fail	0.34		
		pass	0.42					pass	0.21		

All parties agree that these data were obtained from an adequate and well controlled study, and that there is a statistically significant effect of eteplirsen. The disagreement is whether or not the dystrophin production is at a meaningful level that is reasonably likely to predict clinical benefit.

To the extent that one can compare results across studies, these changes in dystrophin are even lower than the values obtained from Study 201/202 (the latter represent the quantity detected at Week 180, not the treatment effect). Dr. Woodcock wrote that “Only 2 of 12 patients achieved a level over 1% of normal control.” Her characterization refers to the amount of protein *detected* at Week 48, not the *change* in protein. In fact, only a single patient out of 12 had a *treatment effect* that exceeded 1%.



3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

Study 201/202 – Data through Week 48

Dystrophin production was assessed in Study 201 using immunohistochemistry, a standard laboratory procedure used primarily to localize proteins in tissue sections, but also used as a semi-quantitative method to measure dystrophin levels. Muscle samples were analyzed at baseline, and at Weeks 12, 24, and 48.

Dr. Woodcock notes “A finding of increased dystrophin was also seen in several IHC assays performed by the applicant.” She explains that several baseline and other pre-Week 180 assays were performed (from Study 201/202), but the validity of the results was questioned at the FDA inspection because of methodological issues, and so she does not consider these data further.

I do not agree with Dr. Woodcock’s outright rejection of these data. In fact, FDA requested a re-reading of the stored images by 3 masked pathologists under improved viewing conditions. We did not request any changes in immunohistochemistry methods or techniques, other than a different approach for selecting microscopic fields for image capture and analysis. Thus, we stressed that their stored images could provide useful data if properly read. The re-read

showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group. (The p -value is nominal because the type-I error rate was not controlled for multiplicity.) Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.

Study 201/202 – Week 180 Data

The applicant performed immunostaining along with Western blot analyses from the skeletal muscle biopsies obtained at Week 180.

Importantly, prior to performing these analyses, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Dr. Woodcock details the technical factors in her memo. Their aim was to determine the treatment effect for each patient, by comparing dystrophin levels at baseline and Week 180. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these samples with muscle tissue from 6 untreated external DMD patients, together to be compared to the Week 180 levels. Images were read by the same 3 pathologists, masked to treatment group.

Because external controls were used, the comparison of pre- vs. post-treatment values suffers from the same problems described for the Western blot analyses (i.e., different patients, different muscles, and possible loss of immunoreactive dystrophin with long-term storage).

These concerns notwithstanding, the applicant claimed a remarkable increase in dystrophin immunostaining at Week 180: the 9 baseline samples (from 3 patients in Study 201/202 and 6 external controls) showed $1.1\% \pm 1.3\%$ positive fibers (mean \pm SD), whereas the Week 180 samples (from 11 patients in Study 201/202) showed $17.4\% \pm 10.0\%$ positive fibers. I will note that FDA made no attempt to inspect or oversee these analyses.

Given that the original analysis showed, at baseline, 13% positive fibers for patients in Study 201/202, it is important to understand why the results from a new immunostaining protocol provided results of 1.1%, an order of magnitude lower.

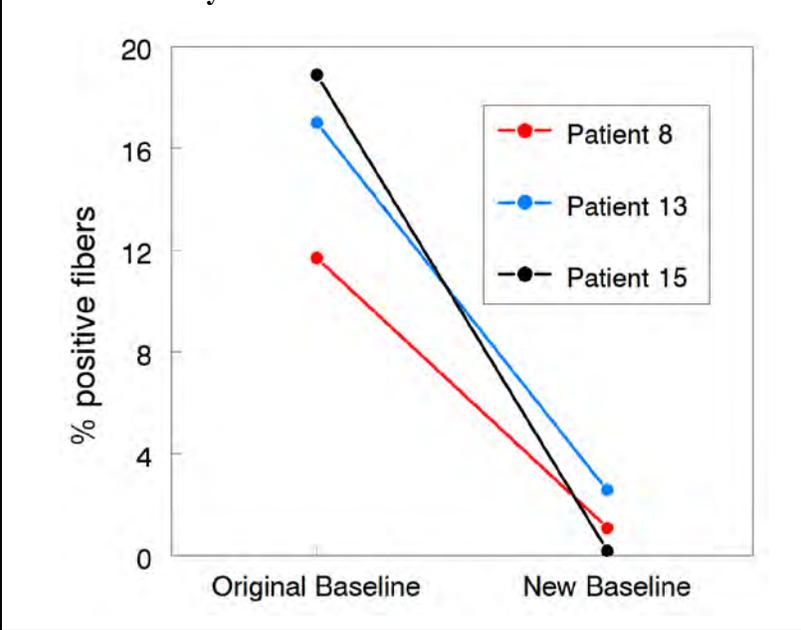
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue from baseline, which permitted a new immunohistochemistry analysis and a comparison of results between the old and new methods. Figure 2 shows how the two methods compare.

These are essentially replicate analyses of a single tissue sample using the two immunohistochemistry methods. There is an inexplicable difference of more than an order of magnitude between results of the old and new immunohistochemistry protocols. Such marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

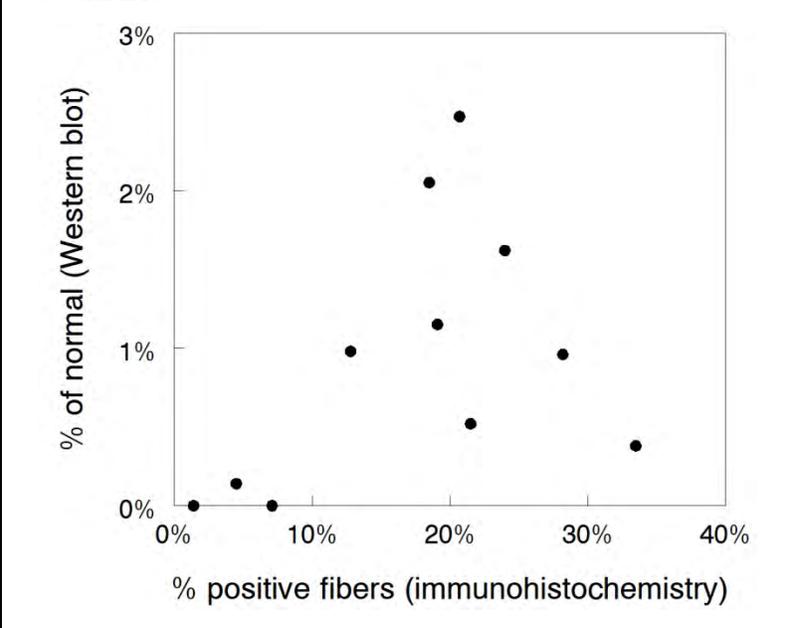
The integrity of the applicant's data is further called into question by lack of agreement between the immunohistochemistry and Western blot methods, i.e., a lack of internal consistency. The applicant claims to have enhanced both the immunohistochemistry methods and the Western blot methods in preparation for processing the Week 180 biopsies. Following these methodological improvements, single tissue blocks were subjected to both analyses – analyses considered to be complementary. Yet the lack of concordance between these two assessments of dystrophin levels is striking (Figure 3).

Figure 2: Comparison of Results from the New and Old Immunohistochemistry Protocols – Lack of Agreement for 3 Patients in Study 201/202



It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, the Western blot methods are inaccurate, or both methods are inaccurate. In light of the discordance between methods, the issues with the control samples, and the order-of-magnitude discrepancy between the old and new immunohistochemistry protocols, these data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Figure 3: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



A critical point is that results of immunohistochemistry analyses are method-dependent, and results from different laboratories are not directly comparable. Here we see a striking difference between results of different methods within a single laboratory.

Dr. Woodcock concluded “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).”

Although this statement does not constitute an important part of her argument in favor of dystrophin production, I do not agree that the immunohistochemistry data show an increase in dystrophin as a result of drug exposure. Given that changes in the immunohistochemistry protocol led to remarkably disparate results, and in light of the lack of correlation between dystrophin results as determined by immunohistochemistry and Western blot, I question the accuracy and interpretability of the Week 180 immunohistochemistry data. Moreover, the results from the properly blinded re-reading of the original data through the first 48 weeks of Study 201/202 are negative. I do agree, however, that the immunohistochemistry images appear to show dystrophin in the proper location, which helps support proof-of-concept.

In summary, I agree that there are data on dystrophin production from one adequate and well controlled study, Study 301, by Western blot. The amount of dystrophin produced and the likelihood of a clinical effect are discussed below.

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

As noted by Dr. Woodcock, “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.”

Without restating the details of Dr. Woodcock’s discussion, I generally agree with her basic summary of the many challenges of interpretation (quoted below). Most of her discussion speaks to the *uncertainties* inherent in correlating dystrophin levels with disease severity. I strongly agree that we lack a sound basis upon which to relate dystrophin levels observed in this development program to observations in the literature.

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

I agree. And importantly, as Dr. Woodcock notes, “the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized.”

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

I will add that the applicant’s own data show a striking difference between results of two somewhat different immunohistochemistry protocols conducted at the same laboratory (Figure 2). Thus, it would be treacherous to try to relate various levels of dystrophin, determined by immunohistochemical methods at various laboratories, to a particular clinical course.

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

Agree. Thus, is not feasible to relate levels of dystrophin determined by older Western blot methods, which lacked, for example, appropriate internal controls, to levels of dystrophin reported in these eteplirsen studies.

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

Agree. It is difficult to predict a protein’s function from its structure; even small changes in dystrophin structure can be important.

“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.”

Agree. There is little consensus on the relationship between dystrophin expression and clinical course at the low levels observed in eteplirsen-treated patients.

I also agree with Dr. Woodcock on the following points, and I paraphrase here:

- Dystrophin levels >10% on Western blot are usually associated with a BMD phenotype. Within the BMD phenotype, the relation between disease severity and protein expression is not clear. Protein quality, rather than quantity, may play a key role in determining phenotype in BMD.
- Patients with DMD are usually found to have undetectable levels of dystrophin, or very low levels. Dr. Woodcock notes that she believes the conventional threshold of <10% protein resulting in DMD was based on immunohistochemistry data. She tries to make a conversion between values observed from immunohistochemistry (~10% points higher on immunohistochemistry than Western blot in DMD) and those observed from Western blot, but I caution that immunohistochemistry results, in particular, are highly method-dependent, as noted above.
- Rarely, dystrophin levels in the 3 to 10% range have been associated with Becker Muscular Dystrophy phenotypes. Dr. Woodcock found no evidence of a threshold value for protein content and expression of a DMD phenotype.

Despite the absence of reliable data, Dr. Woodcock concluded that evidence from Western blot and other experiments shows 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.

Because of the lack of reliable evidence, I do not agree that the small increase in dystrophin shown in Study 301 is ‘reasonably likely’ to predict clinical benefit. This is the central issue in this appeal.

The “reasonably likely” question hinges on whether the protein is functional, and whether the quantity is adequate.

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Nevertheless, the review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as it does in the Becker form of the disease. Although there can be no certainty on this point, the question of function seems small relative to the uncertainty regarding the adequacy of the quantity of protein, and so function is less germane to the question of “reasonably likely.” In short, it is the quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.

At the outset, it must be stated that the minimum quantity of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown.

There are two ways to consider the quantity of dystrophin produced: as a binary responder analysis and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

The problem with a responder analysis is that there are no data upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Here I provide 3 lines of reasoning to support my view that there is not an adequate basis to believe that the small increase in dystrophin shown in Study 301 is reasonably likely to predict clinical benefit: 1) the treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications; 2) the effect size is inadequate on its face; and 3) no evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.

- 1) *The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications.*

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have considered publications from laboratories that attempt to relate particular levels of Becker-type dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Ideally, as suggested by Dr. Woodcock, there would be reliable data showing that Becker-type dystrophin levels in excess of a particular level are associated with a more benign clinical course.

Realistically however, the use of such a framework would be contingent on the ability to make interpretable cross-laboratory comparisons of dystrophin levels, which would require standardized methods to measure dystrophin levels in muscle specimens. Unfortunately, the methods have differed greatly, and the methods in the literature have lacked critical internal controls such as dilution-series. As stressed above, comparison of dystrophin values across laboratories seems unreliable.

With respect to immunohistochemistry analyses, Figure 2 provides ample basis for concern regarding comparability of results using different methods. Results of separate immunohistochemical analyses of skeletal muscle dystrophin, conducted by the same laboratory on single blocks of tissue, differ by more than an order of magnitude. These results underscore the inherent methodological variability of immunohistochemistry assays, and the futility of attempting to compare dystrophin levels across assays/laboratories.

Even with respect to more recent Western blot methods, reproducibility across laboratories is low. As discussed by Dr. Woodcock, Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. The authors found that variability was particularly pronounced with low levels of dystrophin – precisely the area of interest here.

During the applicants' presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, could not have been more clear in warning us not to make comparisons between their Western blot results and reported data in the literature:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In summary, the field has not achieved adequate standardization of methods for dystrophin quantification at the very low levels observed in eteplirsen-treated patients; therefore, it is not valid to compare an increase in Becker-type dystrophin of, at best, 2 to 3%, with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories. *If the applicant's results cannot be compared to results in historical publications, then there is simply no way to determine whether the low dystrophin levels in eteplirsen-treated patients are reasonably likely to predict clinical benefit.*

2) *The effect size is inadequate on its face.*

If one were to assume that it is possible to make cross-laboratory comparisons of dystrophin levels, the *largest* change reliably demonstrated in Study 301, 1.3%, is an order of magnitude less than the minimum dystrophin levels cited to be important in affecting the course of patients with Becker muscular dystrophy (at least 10%).

Some of the better data come from Van den Bergen *et al*, who studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker Muscular Dystrophy (*J Neurol Neurosurg Psychiatry* 2014; 85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their

patients with dystrophin levels <10% showed poor muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Initially, the applicant reported results from immunohistochemistry analyses purportedly demonstrating that eteplirsen caused 50 to 60% positive staining of muscle fibers for dystrophin. This seemingly unprecedented achievement aroused much excitement in the field of DMD research and in the DMD patient community. Upon proper re-analysis, however, the numbers were far lower, and rigorous statistical analyses showed that the changes weren’t statistically significant. The Western blot analysis from Study 201/202 showed a mean dystrophin level of only 0.93% (range 0 to 2.5%), but these values are of questionable reliability. Finally, an adequate and well controlled study (Study 301) showed a mean change of 3-tenths of a percent (range 0 to 1.3%). Given that dystrophin is a structural protein, it seems highly unlikely that such changes would translate to a clinical effect.

Here are Dr. Woodcock’s assertions on this topic:

“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.”

I agree that broad phenotypic distinctions made in the clinic (e.g., Duchenne vs. Intermediate vs Becker Muscular Dystrophy) are different than trying to predict benefit to an individual patient on the basis of a particular change in dystrophin. And I agree that extending ambulation by 6 months to a year (or similar improvements in other functional areas) would be extraordinarily important.

But Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that “...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.” She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit.

3) *No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.*

Dr. Woodcock states:

“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 nonrandomized 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.”

The review team analyzed the clinical data in great detail, and could not reach the conclusion that there was any reliable evidence of improvement relative to the expected natural history of the disease. Study 201 did not show a treatment effect on its 1° clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients (see my review memorandum for more details).

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD, and their vote was in the face of extraordinary pressure from patients and patient advocates to vote for approval. Two of the 3 “yes” votes were from patient representatives.

Correlation between dystrophin production and clinical effect

A correlation between dystrophin production (or with less certainty – dystrophin *detected*) and clinical function could provide some support for a conclusion that dystrophin production is reasonably likely to predict clinical benefit.

The applicant collected data on both dystrophin production and physical performance in Study 201/202. On the basis of the data presented in the NDA, the Division concluded that no patient in Study 201/202 clearly deviated from the natural history of the disease. The Division reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Thus the Division opined that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

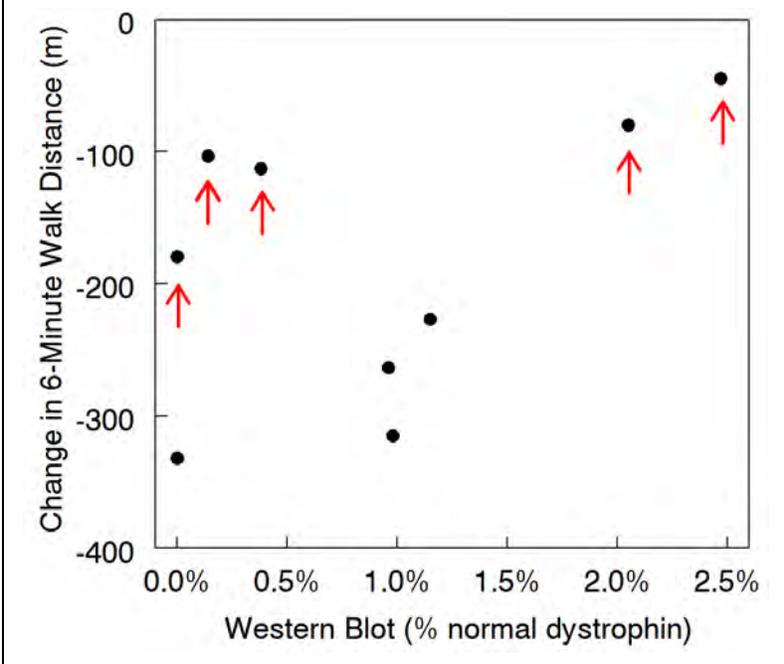
The Division's view notwithstanding, it is worth considering patients on an individual basis to assess the correlation between the quantity of Becker-type dystrophin detected and changes in physical performance.

As noted by Dr. Woodcock, the 6-minute walk test results do not show a strong correlation (Figure 4). For the 9 patients in Study 201/202 who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, the figure shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years.

For the 5 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study (upper right), but 3 had levels that were near-zero (upper left).

Dr. Woodcock also evaluated the North Star Ambulatory Assessment (NSAA) as a function of dystrophin detected in boys who could still walk and who had a dystrophin result at Week 180. She obtained the data from the applicant's briefing document for the Advisory Committee meeting, and found a correlation between dystrophin detected at Week 180 by Western blot and rate of decline in NSAA score through 180 weeks. Her graph is reproduced below:

Figure 4: Study 201/202 – Lack of Correlation between Quantity of Dystrophin Detected and Preservation of Physical Function (6-Minute Walk Distance)



With respect to the correlation, Dr. Woodcock explained: “This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.”

Given that the correlation was driven by the patient depicted at the lower right (blue arrow; dystrophin level =

~2.5%; change in NSAA = 3), I considered the NSAA data from that patient (Figure 6). I found that his course was less benign than would be inferred from a change in NSAA of only 3 units. Specifically, using linear regression (red line in Figure 6), his NSAA score has, instead, worsened by a mean of 2.7 units per year.

I reasoned that inclusion of all of the NSAA data for each patient would provide a more reliable representation of their course than calculating the change between single pre-treatment and post-treatment data points, because of the test-to-test variability (e.g., short-term swings of 4 to 5 points for patient 006). Thus, using linear regression, I calculated the slope of the relationship between NSAA and time for each patient (as per the red line in Figure 6) and plotted the slopes as a function of the dystrophin detected at Week 180. (Slopes were calculated as loss of NSAA units per year.)

Using this method, there was no correlation ($R^2 = 0.36$), Figure 7. Importantly, the slight trend apparent here is driven by one or two data points.

Figure 5: Study 201/202: Analysis of Change in NSAA vs. Expression of Becker-type Dystrophin by Western Blot (Analysis by Dr. Woodcock)

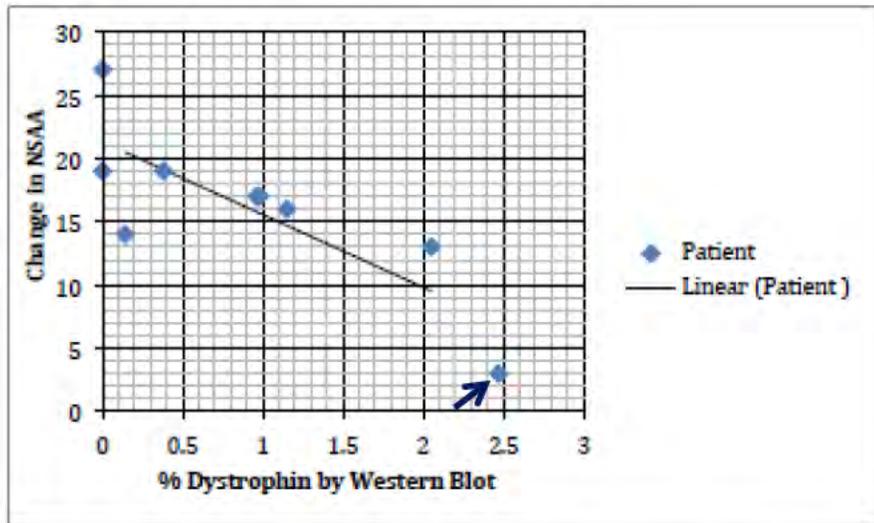
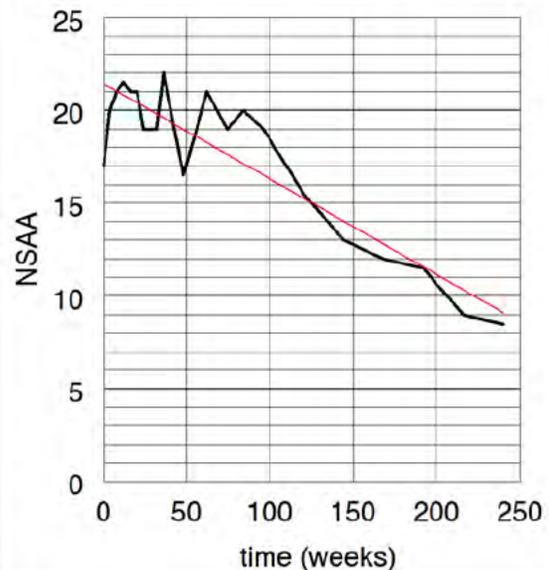


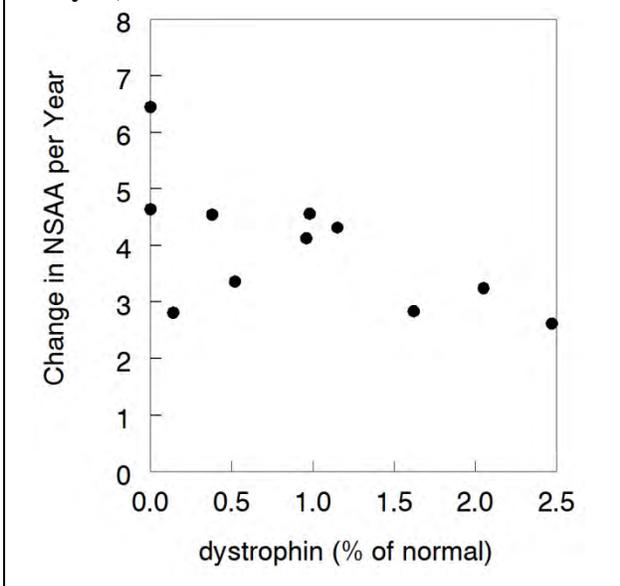
Figure 6: Patient 006: NSAA vs Time



Summary:

In summary, I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%). The levels of dystrophin linked to various Becker Muscular Dystrophy phenotypes in publications are largely not comparable to dystrophin levels measured in this development program. The applicant's interim CEO correctly urged us not to compare data from their Western blot analyses to historical approximations from the literature. And extremely low levels of dystrophin, as found here, seem particularly difficult to quantify and compare across laboratories. Nevertheless, to the degree that findings can be compared across studies, dystrophin levels of 10% or more would need to be achieved to impact the clinical course. The finding in Study 301 is an order of magnitude below this level.

Figure 7: Study 201/202: Analysis of Change in NSAA (Linear Regression) vs. Expression of Becker-type Dystrophin by Western Blot (My Analysis)



Based on protein levels in other deficiency diseases, the effect size here appears to be too small to provide benefit. If dystrophin were an enzyme that catalyzed a biochemical reaction in myocytes, one might posit that a very small quantity could produce a substantial proportion of the minimum necessary reaction product, and that the increase over baseline might be important because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury due to stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. We must also recognize that a treatment that increases dystrophin by 0.3% would seemingly have far less impact than being born with 0.3% more dystrophin, and even *that* seems unlikely to matter.

I can find no precedent of an accelerated approval for a marketing application where the effect size on the surrogate endpoint is as small as 0.3%.

Dr. Woodcock concludes:

“...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....Therefore, I find that the

probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.”

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for demonstration of effectiveness, but this is not true.

Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These facts have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.

Finally, there was no clinical benefit demonstrated in the development program, and the correlation between dystrophin and clinical effect was poor – not surprising given that the applicant provided analyzable data from only 11 patients.

3. Assessment of Possible Impact to Public Health Should My Position Not be Adopted

The approval of this NDA in its present form would have far reaching negative consequences for the public health.

1. Eteplirsen’s risks are certain, whereas its efficacy is not. Having considered Dr. Woodcock’s line of reasoning and her desire to approve eteplirsen, the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs (verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied.

Dr. Woodcock notes that "...the therapy has been relatively safe in the clinic."

The reality is that only a few dozen patients have been exposed to the drug, such that the safety profile is not well characterized. A closely related drug being studied under a (b) (4) With additional experience, important toxicity may emerge for eteplirsen. It is known that many patients in these studies are now receiving infusions through indwelling catheters. Maintenance of vascular access in patients on chronic corticosteroids poses a certain risk of infections. Although we are not yet aware of any infection-related adverse reactions, there would definitely be serious infections and possibly deaths if this drug is marketed, yet evidence of efficacy is lacking.

2. By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

The prospect of providing false hope to desperate patients from a promising but ineffective therapy recalls the experience with *transmyocardial laser revascularization* (TMLR). In the 1990s, patients with coronary atherosclerosis and severe angina who were poor candidates for conventional revascularization procedures ("no-option" patients) underwent a thoracotomy (opening of the chest cavity) to enable use of a laser to create channels through the heart muscle. Ostensibly, these channels provided conduits for blood to flow from inside the left ventricle to the myocardium. Conduct of sham-controlled studies was impossible; studies were essentially baseline-controlled or historically-controlled. Large treatment effects were reported by a number of investigators, generally from small studies. There were marked increases in treadmill exercise time and relief of angina, with effects sustained for more than a year in some cases. Although many in the cardiology community raised concerns about expectation bias and were highly skeptical of the results, to some the effects seemed larger and more durable than could possibly be explained by expectation bias, i.e., a placebo effect. Thousands of patients underwent this invasive procedure with the hope of angina relief. Some years later, with improvements in technology, the conduct of sham-controlled studies became feasible, and TMLR was not found to be effective. The false hope was ultimately dispelled with the publication of two Cochrane Reviews.³ These reviews found the appearance of a marked treatment effect, but 30-day mortality was 6.8% in the TMLR group vs. 0.8% in the no-treatment group. They noted "The assessment of subjective outcomes, such as improvement in angina, was affected by a high risk of bias and this may explain the differences found." In this case, the cost of false hope was ~6% mortality in the first 30 days post-op.

I will also note that the primary endpoint of these laser studies was generally exercise capacity – the same type of endpoint used in the eteplirsen DMD development program, also for "no option" patients.

3. The accelerated approval pathway is designed to expedite the availability of promising new therapies to patients with serious conditions, especially when there are no satisfactory

³ Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003712. DOI: 10.1002/14651858.CD003712.pub3

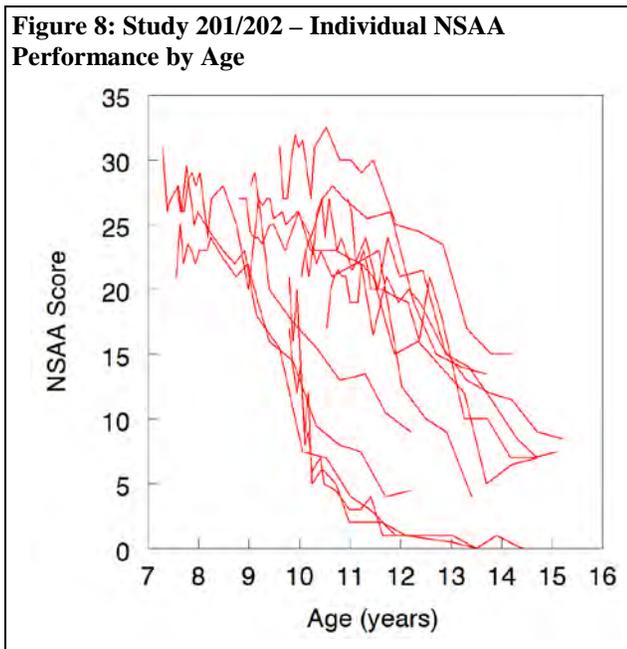
alternative therapies, while preserving standards for safety and effectiveness. For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit, and FDA may withdraw approval of a drug if a trial required for verification of the predicted clinical benefit fails.

In reality, it is difficult to withdrawal a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options. FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval. The reality is that if eteplirsen is given accelerated approval, it is highly likely to remain on the market indefinitely, irrespective of whether or not efficacy is verified.

4. With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression.
5. False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually *are* effective. For example, consider the scenario of a related drug with far greater potential to promote dystrophin production in patients with DMD. In order for a sponsor to study such a drug, patients would likely have to agree to discontinue eteplirsen, and few patients may be willing to do so. In short, approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective, and this impact can be significant.
6. Accelerated approval would lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered “reasonably likely” to support accelerated approval. Similarly, if a ‘responder’ had been defined as a patient with an increase in dystrophin of $\geq 1\%$ (and there is no basis to accept such a low threshold), there would have been only a single responder in Study 301. If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.
7. With accelerated approval of this NDA, there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of

failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.

8. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, we already know this dose is sub-therapeutic. We know this because patients who have been receiving this eteplirsen dose for some 3.5 years have been progressing at a rate that is similar to that expected, based on the natural history of the disease (Figure 8). I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic, when the consequence of a sub-therapeutic dose is clinical deterioration and death. The figure shows the unremitting progression in the patients in Study 201/202, based on changes in NSAA.



9. Approval of this NDA would send the signal that political pressure and even intimidation – not science – guides FDA decisions, with extremely negative consequences (See Grainger D., 11/30/15. “DMD Drugs: an existential threat to FDA,” *Forbes*⁴). The public is well aware of this development program: the meager size of the study population, the marginal (at best) effect size, the Division’s dim view of the efficacy data, and the robust activism of some members of the DMD community. Many would be amazed at an approval action, because other DMD drugs, recently turned down for approval, appeared to provide stronger evidence of efficacy.

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

“Dear Dr. califf: How is it that everyone in and around DMD understands this simple Idea and the science geniuses at FDA don't? You stupid f__ _ers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

⁴ downloaded 7/18/16 at <http://www.forbes.com/sites/davidgrainger/2015/11/30/dmd-drugs-an-existential-threat-to-the-fda/#5ffc712455f7>

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

4. Detailed Description of the History of the Dispute, Including My Description of the Center SDR Procedures Followed and/or Not Followed, Dates of Meetings, and Decisions Rendered Throughout the Process

The following table shows the dates and main activities for 15 Center Director Briefings associated with the development of this drug: 8 Center Director Briefings took place during the IND phase of development, *prior to submission of the NDA*, and 7 Center Director Briefings took place during review of this NDA.

DATE	MEETING	DETAILS
7/17/2013	Center Director Briefing	Follow up on Action Item from 3/13/13 EOP2 Meeting: Sarepta has submitted a comprehensive discussion of the issues from the EOP2 mtg. To discuss the suitability to file the NDA for Subpart H approval.
10/18/2013	Center Director Briefing	Dr. Unger presented an overview and Dr. Farkas had a slide presentation on drisapersen and eteplirsen data. Discussion: 1. Plan to have a manufacturing facility visit by ONDQA - to observe process and obtain yield calculation. Sponsor is expecting to have 2nd batch in Dec 2013. Determine how much product the sponsor has. 2. OBP: recommended to establish specificity of the antibody and variability of the assay. 3. Next trial - plan to have OSI group to observe the conduct. 4. Need data from the GSK (drisapersen) trial. DNP has previously requested the Phase 3 topline data from GSK, but did not get any response. Dr. Woodcock will initiate an inquiry to the sponsor (raw data). 5. The Agency needs to assist Sarepta (characterize biomarker, CMC facility, observe 6MWT, etc.) 6. 2nd Internal Meeting (Drs. Woodcock, Temple, Jenkins, Unger and Neuro) before the 11/8/13 sponsor meeting. Discuss further what to convey to Sarepta.
10/28/2013	Center Director Briefing (continuation of 10/18/13 meeting)	Suggestions/Recommendations for DNP to Consider: -- We have concluded that we will not ask for biopsy until (we understand the histopathology and are) we're certain what is a quantitative measure and identified the surrogate marker for the study. -- Tell the sponsor that we have changed our view for the quantitative measure of truncated dystrophin as a surrogate PD marker used in their study, because of the recent natural history

		<p>study and failure of the drisapersen trial from GSK.</p> <p>-- Dr. Woodcock wants to have a comprehensive literature review to fully understand what's this mean of the deletions, mutations, or duplications in the dystrophin gene, or this exon 51 of dystrophin mRNA ((Office of Translational Science) believe this task was assigned to a different group).</p> <p>-- To ask the Sponsor to provide their production schedule. I believe Dr. Woodcock wants to understand the amount of production and determine if the company can provide the drugs to those DMD patients in the future.</p> <p>-- To suggest that the Sponsor consider enrolling patients younger in age (like starting with 5yrs) in their clinical study.</p> <p>-- To ask the Sponsor if they could provide drugs for compassionate use to patients (who are very sick or those were in the drisapersen trial previously).</p> <p>-- Schedule a T-con with GSK to discuss biomarker data</p>
1/17/2014	Center Director Briefing	Request: Team to present DMD drugs study design to Dr. Woodcock – Path forward for Sarepta (& GSK)
2/6/2014	Center Director Briefing	DMD drugs study design (Discuss Sarepta path forward) Action items: (a) Request biomarker data from the sponsor - done TC on 2/7/14(b) If data interpretable, meet with sponsor for a brainstorming session. Then follow-up with Advice Letter
3/5/2014	Center Director Briefing	Dr. Ash Rao presented biomarker data findings (including Drs. Woodcock, Jenkins, Temple, Unger, Moscicki) Team discussed path forward. Action Item: to invite Sarepta for a brainstorming discussion.
3/19/2014	Sponsor Meeting, with Center Director	brainstorming discussion - study design and path forward Action: Sarepta to submit proposed studies and next steps
4/2/2014	Center Director Briefing	Drs. Woodcock, Moscicki, Temple, Unger Discuss proposal & comments to sponsor ~Advice Letter-include previous meeting discussions ~FDA workshop – biomarker ~Work w/ sponsor on dystrophin biomarker ~Natural history raw data - primary investigators
6/26/2015		SUBMISSION OF NDA
12/9/2015	Center Director Briefing	To brief on the current status of eteplirsen review in advance of the planned Jan 22, 2016 AC meeting. To discuss the application and the plan of action.
1/13/2016	Center Director Briefing	To review the slide presentation and plan of action for eteplirsen, that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership.
2/10/2016	Center Director Briefing	To discuss the ongoing review of the NDA, and what will be presented during the Advisory Committee Meeting in April. To discuss the strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.
4/15/2016	Center Director Briefing	To discuss the statistical review of the CINRG data. To discuss the review of data on DMD that was conducted by the Cooperative International Neuromuscular Research Group
4/25/2016	Advisory Committee Meeting	
5/4/2016	Center Director Briefing	Discuss the outcome and plan of actions for the application post advisory committee meeting

5/31/2016	Center Director Briefing	Discuss reviews conducted by the review team and leadership along with any additional information obtained from the sponsor. Discussed Dr. Woodcock's memo. Timeline for reviews due to Dr. Woodcock.
7/6/2016	Center Director Briefing	<ol style="list-style-type: none"> 1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be "reasonably likely to predict clinical benefit" and used as a surrogate endpoint to support accelerated approval. 2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval. 3. Description of the available clinical data in the drug label if approved.

Based on my years of experience in Office of Drug Evaluation-I, the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented. She also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.

There is no question that there has been adequate time and place for the discussion of various views. I will note, however, that I found it unfortunate that the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already "...reached a different conclusion...." than the review team.

5. Action, Decision or Remedy Sought

Although the above paragraph could be considered grounds for an appeal based on process, I seek instead a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit. I maintain, along with the Division of Neurology Products, Office of Biometrics, Office of Clinical Pharmacology, Office of New Drugs, and the majority of the members of the Peripheral and Central Nervous System Drugs Advisory Committee, that substantial evidence is lacking to support either a conventional or accelerated approval, and that a *complete response* should be issued for this NDA.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will eventually be capable of ameliorating the fundamental genetic defect of DMD, but the effect size here is insufficient at the tested doses.

6. Path Forward

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at doses of 30 and 50 mg/kg/week are fairly solid, but they do not support efficacy.

I remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the primary endpoint, again, testing higher doses.

The applicant is continuing to enroll Study 301 (PROMOVI), an open-label, multicenter, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

My suggestion for a path to approval is to randomize patients in the ongoing Study 301 to:

- 1) either remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blinded to treatment group. For accelerated approval, the primary endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the primary endpoint would be a test(s) of physical performance such as NSAA or rise time.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, would want to know whether higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients randomized to placebo, this would not be a concern here with all patients receiving active drug. And I would recommend that the applicant forego immunohistochemistry studies in favor of Western blot analyses, such that needle biopsies with local anesthesia would be sufficient (rather than open biopsies with more intensive anesthesia and greater morbidity).

I also believe that it would be desirable for the company to provide access to eteplirsen for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

From: Unger, Ellis
To: Behr, Virginia L; Woodcock, Janet; Temple, Robert; Dunn, Billy; Bastings, Eric; Jenkins, John K; Farkas, Ronald; Breder, Christopher D
Cc: Choy, Fannie (Yuet); Lowy, Naomi; Locicero, Colleen L; Mazur, Julia
Subject: RE: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)
Date: Monday, July 18, 2016 12:23:28 AM
Attachments: NDA 206488 Office Director Memo 7-16-16.pdf

I just realized that my memo wasn't attached. Here it is.

Ellis

From: Unger, Ellis
Sent: Saturday, July 16, 2016 1:42 PM
To: Behr, Virginia L; Woodcock, Janet; Temple, Robert; Dunn, Billy; Bastings, Eric; Jenkins, John K; Farkas, Ronald
Cc: Choy, Fannie (Yuet); Lowy, Naomi; Locicero, Colleen L; Mazur, Julia
Subject: RE: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)

All,

I've just DARRTed my eteplirsen review. Thanks for all of your hard work and thoughtful input. I've made a number of changes since the last draft.

Ellis

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Saturday, July 16, 2016 1:38 PM
To: Unger, Ellis; Leginus, Joseph; Myers, Deborah; Woody, Dahlia; Miller, Denise; Rogers, Hobart; El Hage, Antoine N; Maduro, Ruth; Ling, Xiang; Wu, Ta-Chen; Chelliah, Mariappan; Braver, Elisa; Bhattaram, Atul; Hawver, David; Breder, Christopher D; Choy, Fannie (Yuet); Flowers, Charlene M; Rao, Ashutosh
Subject: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)

[Proceed to DARRTS Welcome Screen](#)

Finalized - Office Director Review (REV-SUMMARY-11)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
REV-SUMMARY-11	SUMMARY	Office Director Review

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Submission Number	Submission Classification	Group ID
NDA-206488	SAREPTA THERAPEUTICS INC	Eteplirsen	ORIG-1	Type I- New Molecular Entity	

Signers

Signer	Proxy Signer	Signed Status	Signed Date
UNGER, ELLIS F.		signed	07/16/2016



Office of Drug Evaluation-I: Decisional Memo

Date	July 15, 2016
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	206488
Applicant Name	Sarepta Therapeutics
Date of Submission	June 26, 2015
PDUFA Goal Date	May 26, 2016 (post-3-month extension for major amendment)
Proprietary Name/ Established (USAN) Name	EXONDYS 51™ eteplirsen injection
Dosage Forms/ Strengths	2 mL single-use vials containing 100 mg (50 mg/mL) eteplirsen 10 mL single-use vials containing 500 mg (50 mg/mL) eteplirsen
Indication originally sought by applicant (see page 29 for final)	“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials.”
Action:	<i>Complete response</i>

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Yuet (Fannie) Choy, Laurie Kelley
Medical Officer/Clinical	Christopher Breder
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, Ta-Chen Wu, Hobart Rogers, Kevin Krudys, Angela Men, Christian Grimstein, Mehul Mehta
Statistical Review	Xiang Ling, Kun Jin, Hsien Ming (Jim) Hung
Pharmacology Toxicology	David Hawver, Lois Freed, Paul Brown
Office of Biotechnology Products	Ashutosh Rao, Amy Rosenberg
Office of New Drug Quality Assessment	Joseph Leginus, Mari Chelliah, Sung Kim, Denise Miller, Zhong Li, Dahlia Woody, Martha Heimann, James Laurensen, Donna Christner, Neal Sweeney, Edwin Jao, Zhihao Peter Qiu, Wendy Wilson-Lee, M. Scott Furness
Office of Scientific Investigations	Antoine El Hage, Cara Alfaro, Susan Thompson, Kassa Ayalew, Ni Aye Khin
Method Validation	Michael Hadwiger, Michael Trehy
Statistical Review – Stability data	Zhuang Miao, Xiaoyu Dong, Meiyu Shen, Yi Tsong
Office of Prescription Drug Promotion	Aline Moukhtara
Division of Medication Error Prevention and Analysis	Deborah Meyers, Justine Harris, Danielle Harris, Todd Bridges
Division of Risk Management	Robert Pratt, Jamie Parker, Kellie Taylor, Cynthia LaCivita
Associate Director for Labeling	Tracy Peters
Cross-Discipline Team Leader	Ronald Farkas
Deputy Director, Division of Neurology Products	Eric Bastings

1. Introduction

Sarepta Therapeutics is seeking accelerated approval for eteplirsen for the proposed indication:

“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials.”

I agree with the views of the Division of Neurology Products (DNP), the Office of Biometrics, and the Office of Clinical Pharmacology that the applicant has not provided substantial evidence of effectiveness from adequate and well controlled trials to support conventional approval. I also agree that the applicant has not provided support for accelerated approval, i.e., evidence from adequate and well controlled trials of an effect on a biomarker that is reasonably likely to predict effectiveness. Thus, I agree with the DNP recommendation to issue a *Complete Response* for this application.

2. Background

Description:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, restoration of the mRNA reading frame would permit translation of an internally truncated, but nevertheless functional form of the dystrophin protein. The drug is targeted specifically for patients with DMD “who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.” It is not clear which of the specific mutations are amenable to exon 51 skipping.

PMOs are a class of synthetic molecules based upon a redesign of the natural nucleic acid structure. They are distinguished from native DNA and RNA because of a 6-membered morpholino ring that replaces the 5-membered ring found in native DNA and RNA. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in native DNA and RNA. Each morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10.3 kilodaltons.

Disease Background:

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene located on the short arm of the X chromosome. These mutations disrupt the mRNA reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys (~1 in 10,000 to 14,000 males). Patients who are amenable to skipping exon 51 constitute ~13% of the DMD patient population.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix, and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Currently, glucocorticoid therapy is the cornerstone of clinical management, and is widely believed to delay loss of ambulation and respiratory decline by several years. Ventilatory assistance and physiotherapy are also thought to improve survival for DMD patients.

3. Product Quality

From a product quality perspective, NDA 206488 is recommended for approval. Eteplirsen would be marketed as a sterile, aqueous, preservative-free, concentrated solution for dilution prior to IV administration, to be supplied in single-use glass vials containing 100 mg or 500 mg eteplirsen (50 mg/mL).

OPQ recommends the following post-marketing commitments (PMCs), to be fulfilled no later than one year following NDA approval:

1. Investigate the root cause of the increasing assay trend observed in the drug product stability study.
2. Revalidate the accuracy of the in-process (b) (4) method used during drug product manufacture.
3. Revalidate the robustness of the in-process (b) (4) method in terms of (b) (4) (b) (4).
4. Investigate the consistent bias in the in-process (b) (4) results and the release (b) (4) (b) (4) results.

4. Nonclinical Pharmacology/Toxicology:

From a nonclinical perspective, NDA 206488 is recommended for approval. Pivotal toxicology studies were conducted in male monkeys (39-week study) and juvenile male rats (10-week study). A 26-week study was conducted in male transgenic mdx mice using a mouse-specific surrogate (AVI-4225). In all 3 species, the kidney was identified as the 1° target organ, with dose-dependent renal tubular cytoplasmic basophilia and/or vacuolation and tubular degeneration and necrosis, primarily at the highest doses tested.

Dilatation of the lateral ventricles of the brain was observed at mid and high doses in the *mdx* mouse study. The mechanism of this effect and its relevance to humans are unknown. In juvenile rats, slight reductions in bone length, width, area, mineral content, and mineral density were observed at the high dose. These concerns could lead to recommendations for long-term monitoring in patients.

Mean eteplirsen plasma exposures (AUC) at the no observed adverse effect levels (NOAELs) for monkeys and juvenile rats were 20- and 6-fold, respectively, higher than that of patients who received the to-be-marketed dose of 30 mg/kg/week by the intravenous route.

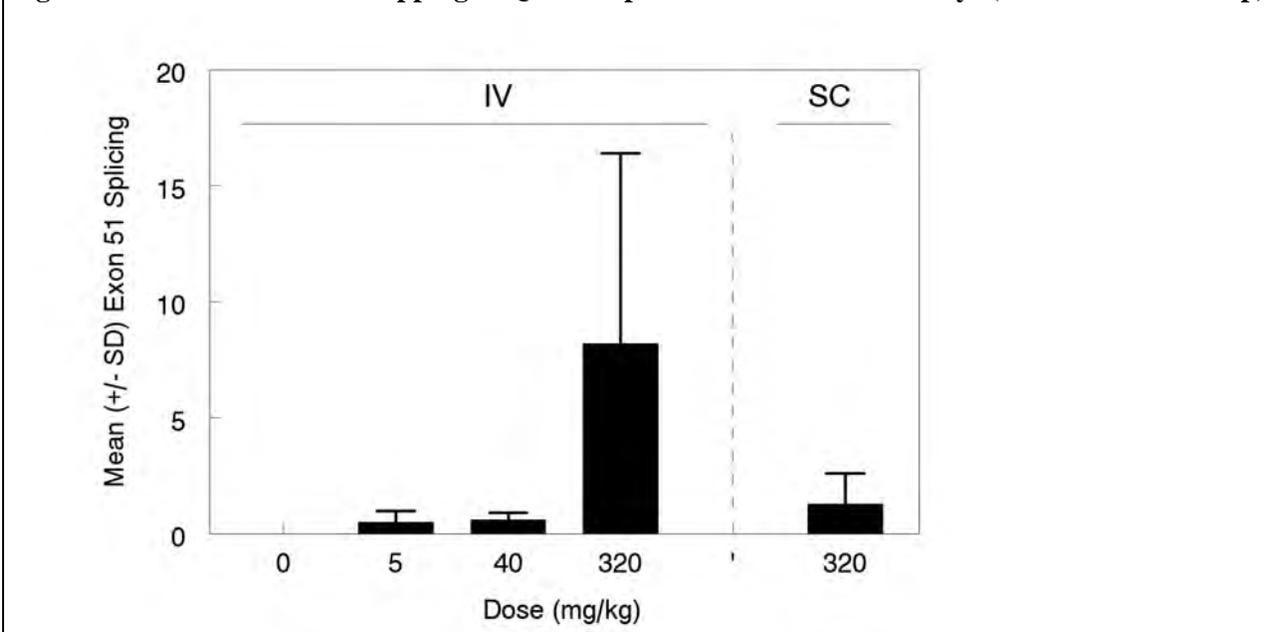
The applicant presented data on the exon skipping activity of eteplirsen in cynomolgus monkeys (“Exon skipping activity of AVI-4658 in cynomolgus monkey tissue samples from ^{(b) (4)} study ^{(b) (4)},” applicant study 4658-ssa-005). Samples of quadriceps muscle, heart, and diaphragm tissues were collected on Day 79 from cynomolgus monkeys after 12 weekly doses of eteplirsen at 0, 5, 40, or 320 mg/kg IV, or 320 mg/kg SC. Muscle samples were analyzed for exon 51 skipping of the dystrophin gene using polymerase chain reaction (PCR).

Exon skipping was detected in a nonlinear, dose-dependent manner (Table 1, Figure 1). With a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. As noted below, the applicant studied doses of 30 and 50 mg/kg/week in the clinic (6 patients at each dose), and there is significant question as to whether the plateau of the dose-response curve was reached. It is possible that much higher doses could lead to substantially greater effects on dystrophin production – effects that could be important for efficacy.

Table 1: Average Percentage of Exon 51 Skipping in Intact Monkeys (N=8 for Each Group)

Tissue	Average % Exon 51 Splicing ± SD				
	0 mg/kg IV	5 mg/kg IV	40 mg/kg IV	320 mg/kg IV	320 mg/kg SC
Quadriceps muscle	0.0 ± 0.0	0.5 ± 0.5	0.6 ± 0.3	8.2 ± 7.4	1.3 ± 0.5
Heart	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.2	4.5 ± 2.9	1.4 ± 0.5
Diaphragm	0.0 ± 0.0	0.2 ± 0.2	0.9 ± 0.7	6.1 ± 3.5	2.2 ± 0.9

Figure 1: Evidence of Exon Skipping in Quadriceps Muscle in Intact Monkeys (N=8 for Each Group)



With respect to the advisability of evaluating higher doses in humans, this subject is well summarized by Dr. Bastings in his Division Memo: “Considering the seriousness of DMD, the unmet medical need, and the nature of the toxicities observed in animals, I believe that the nonclinical data would support, with proper monitoring, dosing in DMD patients at least up to 200 mg/kg, a dose expected to provide exposure similar to the most sensitive species NOAEL for the toxicities seen in animals. If the human safety experience at these doses is acceptable, further dose escalation is possible in DMD patients.”

Finally, the nonclinical review team provided insight that is relevant for the interpretation of clinical data with respect to production of dystrophin protein: “The most robust finding among the studies provided and referenced in this submission was the wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients.”

Carcinogenicity:

Carcinogenicity studies have not been conducted with eteplirsen. The nonclinical review team opined that carcinogenicity studies in 2 species should be conducted as a post-marketing requirement. Dr. Bastings agrees, and I agree, that for this serious indication with unmet need, carcinogenicity studies can be deferred until after marketing.

5. Clinical Pharmacology

The Clinical Pharmacology team does not recommend approval; they recommend generation of robust evidence of effectiveness prior to approval. Specifically, the team is recommending a double-blind, placebo-controlled study in patients with mutations amenable to exon-51 skipping who are likely to be ambulant for 1 year, with use of appropriate endpoints based on upper or lower body strength in patients between 4 and 12 years of age. They also suggest study of doses greater than 50 mg/kg administered weekly, or alternate regimens that would include loading and maintenance doses, for example, twice-weekly administration for 6 months followed by weekly administration for 6 months. Their recommendations are based on the 3- to 4-hour half-life of the drug, urinary excretion of 60-70% of the drug within 24 hours, and the absence of known toxicity at doses of 50 mg/kg. The immunogenicity of eteplirsen can be further assessed in future clinical trial(s) as well.

Summary of Pharmacokinetics:

- Pharmacokinetics was approximately dose-proportional and linear from 0.5 to 50 mg/kg/week, with insignificant accumulation in this dose range.
- Following single or multiple intravenous infusions, peak plasma concentrations (C_{max}) occurred near the end of infusion.
- Plasma concentration-time profiles showed multi-phasic decline, with virtually all drug eliminated within 24 hours (24 hours after completion of infusion, eteplirsen concentrations were 0.02% of C_{max}).
- At doses of 30 and 50 mg/kg, the elimination half-life is ~3.5 hours, with ~65% of the drug excreted unchanged in the urine. The drug is not metabolized.
- Protein binding of eteplirsen in humans is relatively low, ~6% to 17%, and is independent of concentration.

- The volume of distribution data suggest distribution or cellular uptake into peripheral tissues.
- Inter-subject pharmacokinetic variability is moderate, generally in the range of 20 to 55% for exposure measures (C_{max} and AUCs) as well as other key pharmacokinetic parameters.
- Intrinsic factors were not studied (typically, in a larger development program, age, gender, body weight, geographic region, hepatic impairment, renal impairment, and other potentially significant covariates would be studied).
- *In vitro* investigations on major CYP isozymes and transporters did not reveal the need for additional investigation in humans.
- Eteplirsen was not a significant inhibitor or inducer of CYP.
- Eteplirsen was not a substrate or inhibitor for any of the key human transporters tested.
- Eteplirsen is expected to have a low potential for drug-drug interactions.

Finally, the clinical pharmacology team noted that if eteplirsen were found to be safe and effective, it would likely benefit all mutations amenable to exon-51 skipping and should be labeled accordingly.

QT Effects:

QT effects were not formally investigated in man.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

Sarepta is seeking accelerated approval for eteplirsen for the proposed indication:

“EXONDYS 51 is indicated 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. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see *Clinical Studies (14)*]. Continued benefit will be evaluated through confirmatory trials.”

In this section, I provide an explanation of how accelerated approval might be used as a potential pathway to approval, based on production of dystrophin in skeletal muscle. I then discuss the evidence that eteplirsen produces dystrophin in skeletal muscle, based on immunohistochemistry and Western blot analyses. Finally, I discuss the clinical data that could serve as the basis for a conventional approval.

Accelerated Approval:

The applicant has requested accelerated approval based on an endpoint of 6-minute walk distance. The proposed indication states that 6-minute walk test is considered to be an intermediate endpoint demonstrating delayed disease progression.

There is little in the NDA to explain the applicant’s thought process here. In Sarepta’s briefing materials for the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, they stated (page 16):

“The accelerated approval pathway means that there will be an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty is addressed by the requirement that ‘appropriate post-approval studies to verify and describe the predicted effect’ would usually be underway at the time of approval.”

The applicant appears to misconstrue the intent of the accelerated approval pathway. They purport to show that, after 36 months of treatment, eteplirsen improves physical performance as assessed by the 6-minute walk test. We consider the 6-minute walk test to be a valid and meaningful measure of how well a patient functions – i.e., a clinical endpoint that would be a basis for full approval – not a surrogate endpoint or an intermediate endpoint. For slowly progressive diseases, an intermediate clinical endpoint, a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug’s effect on irreversible morbidity or mortality or other clinical benefit, can be used to support accelerated approval. But all would agree that showing an improvement on a clinically meaningful endpoint at 36 months would be adequate to support a conventional approval in DMD, a position we have taken with other DMD drugs.

Thus, the applicant has provided study results that purport to show improvement in a meaningful clinical endpoint after a relatively long duration of treatment, but they appear to propose accelerated approval as a means to deal with uncertainty about whether the therapy has actually been shown to provide a clinical benefit in the trial.

Clearly, if the review team had reached the conclusion that the applicant had provided substantial evidence of an effect on 6-minute walk distance during some 3 to 3.5 years of treatment, they would recommend a conventional (full) approval, and not accelerated approval. As noted in the reviews, however, for a number of reasons the review team does not believe that the applicant has provided substantial evidence of an effect on 6-minute walk distance, or any measure of physical performance (see below). Importantly, accelerated approval is not intended to enable use of less than substantial evidence of a treatment effect as a basis for approval, to be bolstered by more compelling evidence to be developed in the post-marketing setting.

Despite the lack of substantial evidence of clinical efficacy from Study 201/202 (see below), it is important to consider whether accelerated approval, based on an effect on a surrogate endpoint, could provide a viable alternative pathway to approval. The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept “...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological,

pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 3) whether the effect demonstrated meets the test of being “reasonably likely” to predict clinical benefit.

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for the demonstration of effectiveness, but this is not correct. Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These requirements have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

Again, the critical issue here is whether factor 3 (above) is met, in light of these considerations.

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. (Of note, the best-case scenario for eteplirsen is the production of an abnormal Becker-type dystrophin, not normal dystrophin, but that will be discussed later.)

The second part of factor 3 is whether an effect has been demonstrated, and the standard remains ‘substantial evidence’ based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05.¹

¹ In some situations, FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness. See: “Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;” May, 1998.

The third part of factor 3, the determination that the demonstrated effect is “reasonably likely” to predict clinical benefit, is a matter of judgment. Thus, once there is substantial evidence of a treatment effect, the determination of whether the effect size is “reasonably likely” to predict clinical benefit is an area where flexibility can be applied. Presumably there is some threshold effect that would have to be achieved in order to satisfy this criterion, but this is not described in the regulations.

Is There a Basis for Accelerated Approval: Production of Dystrophin Protein in Skeletal Muscle?

The applicant assessed skipping of the messenger RNA exon using reverse transcriptase polymerase chain reaction (RT-PCR), a standard laboratory technique to detect RNA expression. Exon 51 skipping was confirmed by RT-PCR analysis in all patients treated with eteplirsen, establishing proof of concept that eteplirsen can cause at least some degree of exon 51 skipping, as intended. Because PCR is a highly sensitive technique that can detect even a few copies of messenger RNA, the findings do not support efficacy.

Dystrophin production was assessed by two widely-used and complementary methods: immunofluorescence (immunohistochemistry) and Western blot. Immunofluorescence is generally used to assess the presence or absence of proteins in tissue sections, and is particularly useful for cellular localization of protein (by light microscopy). Western blot provides quantitative analysis of protein, but no information on cellular localization.

Originally, the applicant evaluated the effect of eteplirsen on dystrophin expression in Studies 28, 33, and 201/202.

Of note however, as the May 26, 2016 goal date was approaching, the Office of New Drugs (OND) and the Center for Drug Evaluation and Research (CDER) could not reach agreement on the regulatory action for this NDA: the Office of New Drugs favored issuance of a complete response whereas CDER favored approval.

Thus, in order to obtain definitive data on dystrophin production to support accelerated approval, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in the ongoing Study 301 (PROMOVI). The applicant was told by CDER that if they were “...successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval....” Thus, data from Study 301 were included in this NDA and discussed below.

A. Immunohistochemistry

The applicant used immunohistochemistry in cross-sections of skeletal muscle biopsies to distinguish and count “dystrophin-positive” and “dystrophin-negative” muscle fibers. The methods are described in detail in Dr. Breder’s review. Briefly, following immunostaining of tissue sections for dystrophin, 4 fields were manually selected from the 4 quadrants of each slide, and images were captured (digitized) at 20X magnification. The contrast of each image was manipulated to enhance background staining so that most of the muscle fibers became visible, making it possible for the reader to perform a manual count of the total number of fibers. Image contrast was returned to normal, and positive fibers – fibers with at least some degree of

positive staining – were manually counted. For each field, the number of positive fibers was divided by the total number of fibers to calculate the percentage of positive fibers. Various rules were prospectively established to define “positive” fibers; in essence, a fiber could be classified as “positive” if its staining intensity was only slightly perceptible over background. Importantly therefore, a reading of 50% “positive” fibers in a tissue field is not tantamount to 50% (normal) dystrophin. A 50% figure means only that half the fibers exhibited staining that was at least barely perceptible over background.

Immunofluorescence data were also analyzed using Bioquant software. For these analyses, the user determined a brightness threshold for each digitized image, in essence selecting all pixels where staining intensity exceeded a particular user-selected value. Once selected, the software calculated the mean intensity of the selected pixels. Given that the region of interest for these analyses was limited to the pixels that exceeded a threshold rather than the total image, I do not consider the Bioquant analyses to be readily interpretable.

Study 33 was a 7-patient, exploratory, phase 1 study, initiated in 2007 at the Hammersmith and Saint Mary’s Hospitals, London, UK. Two subjects received a single 0.09-mg dose of eteplirsen in the extensor digitorum brevis (EDB) muscle of one foot and placebo in the contralateral foot. Five subjects received a single 0.9-mg dose of eteplirsen in the EDB muscle of one foot and placebo in the contralateral foot. After 14 to 28 days, dystrophin was detected adjacent to the needle tracks by immunohistochemistry and Western blot. Western blot analyses were not carried out for control muscles injected with placebo.

Study 28 was a 19-patient, exploratory, phase 1 study, initiated in 2009 at 2 sites in the UK. Patients had DMD amenable to exon 51 skipping. Eteplirsen was administered weekly by the intravenous route for 12 weeks at doses ranging from 0.5 to 20 mg/kg. There were up to 4 patients per dose level. After FDA expressed concerns about the reliability of the procedures and methods, the applicant responded that “Study 28 was an exploratory phase 1b study which was only intended to generate proof of concept data to guide future studies. For this reason, quality controls for the dystrophin data in Study 28 were not properly optimized.” Some data were missing, and after considering all of this information, the review team did not deem the results to be interpretable.

Study 201 was a single-center, double-blind, placebo-controlled, parallel-dose study in 12 patients with DMD. The study was initiated in 2011. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. The extension trial is well described in other reviews.

The 1^o endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry. The main comparison was planned to be the 50 mg/kg/week group at Week 12 and the 30 mg/kg/week group at Week 24 to the combined placebo group. The applicant’s original results are shown in Table 2, adapted from their clinical study report. As will be noted below, these results are not deemed to be reliable.

Table 2: Adapted From Table 11-1 of Applicant’s Clinical Study Report: Effect of Eteplirsen on Dystrophin-Positive Fibers Detected by Immunohistochemistry with MANDYS106

Time point		Placebo N = 4	30 mg/kg/wk Eteplirsen N = 4	50 mg/kg/wk Eteplirsen N = 4
Baseline	Mean	15.64	18.19	11.00
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment^b	Mean	11.59	41.14	11.79
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95 ^c	0.79
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4

It should be stressed again that the figures in the table represent the percentage of dystrophin-positive fibers, but in no way correspond to the percentage or quantity of dystrophin relative to a normal individual. Muscle fibers displaying virtually any staining intensity above background were considered “positive.” As noted above, therefore, a reading of 50% positive fibers means only that 50% of fibers exhibited staining that was perceptively above background.

These results were substantially reported in a 2013 publication,² which claimed that eteplirsen markedly increased functional dystrophin production: “...the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

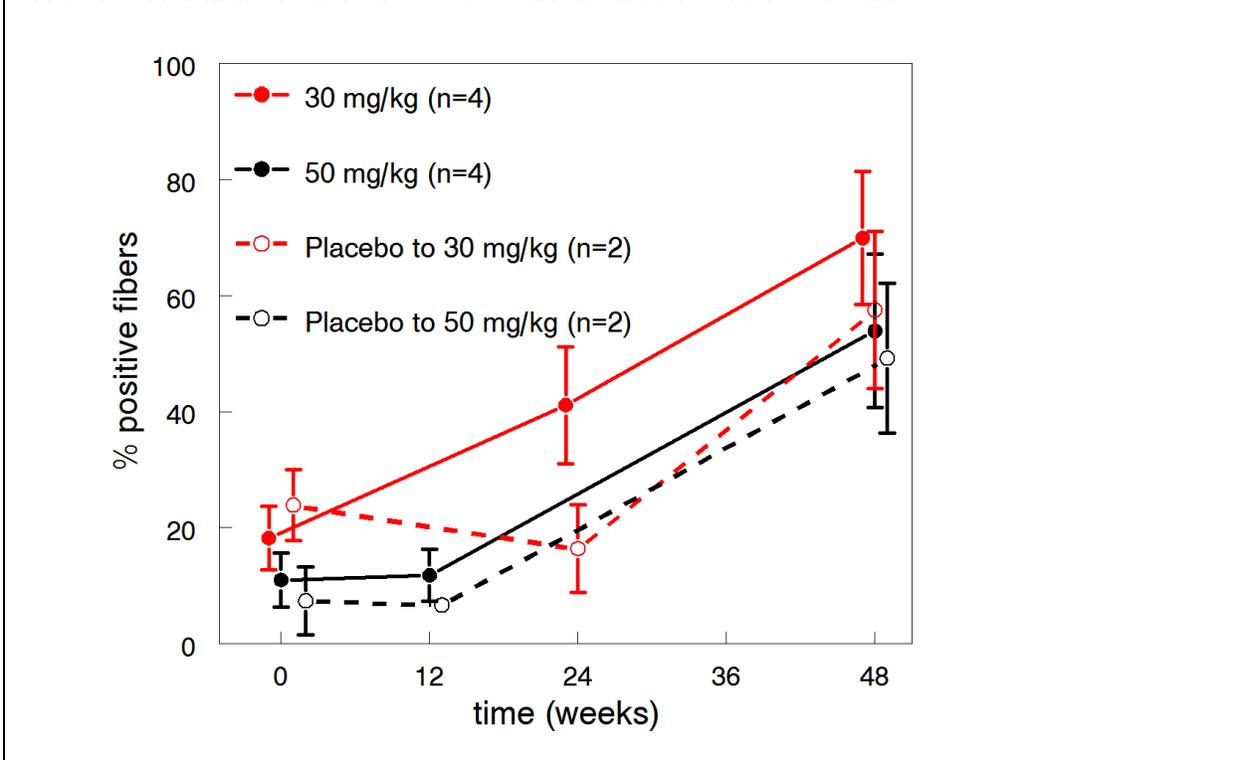
Publication of this paper was followed by a Sarepta press release,³ which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community. It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible (see below).

² Mendell JR, et al: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47

³ Sarepta press release, 8/8/13, at <http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1846052> [downloaded 5/10/16]

The original data from Nationwide Children’s Hospital submitted to FDA are plotted in Figure 2. Immunostaining for dystrophin appears to increase markedly in all 4 groups with time, with some 50 to 60% of fibers staining positive for dystrophin at 48 weeks. For reasons explained below, the review team disagrees with the veracity of these data.

Figure 2: Original Results of Dystrophin Immunostaining Using MANDYS106 Antibody: Percent Positive Fibers as a Function of Time – Results Not Verified on Re-read



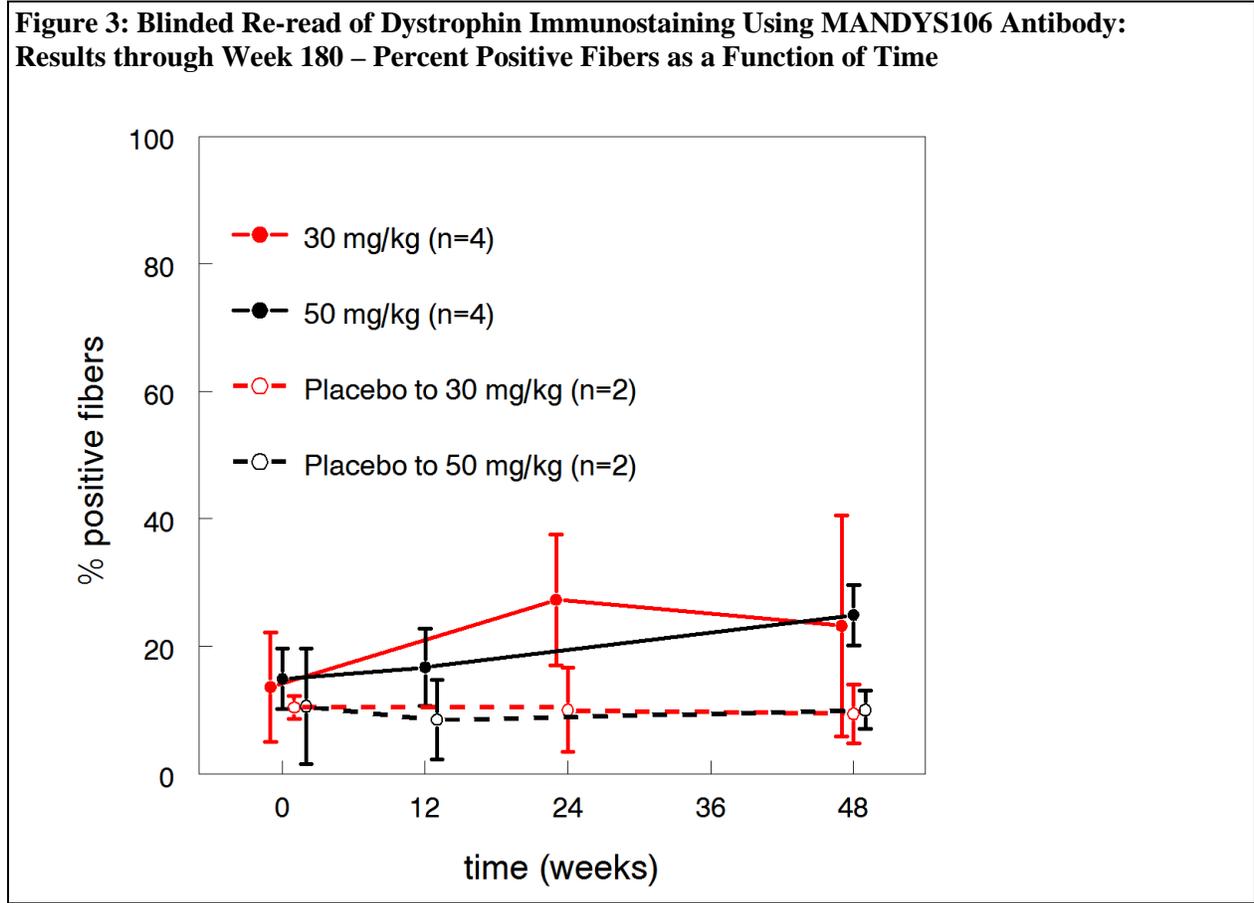
I was part of an inspection team that conducted (May 29 and 30, 2014) a site visit to Nationwide Children’s Hospital in Columbus, OH, where Study 201 was conducted. We found the analytical procedures to be typical of an academic research center, seemingly appropriate for what was simply an exploratory phase 1/2 study, but not suitable for an adequate and well controlled study aimed to serve as the basis for a regulatory action. The procedures and controls that one would expect to see in support of a phase 3 registrational trial were not in evidence.

Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had been read by a single technician using an older liquid crystal display (LCD) computer monitor in a windowed room where lighting was not controlled. (The technician had to suspend reading around mid-day, when brighter light began to fill the room and reading became impossible.) These issues are well described in a summary of inspectional findings in Dr. Breder’s clinical review (page 27). There was also concern that the reader, although masked to treatment assignment, was not masked to sequence/time (see below). Importantly, in a trial where all patients eventually received the active drug, knowledge of sequence could lead to the false appearance of a treatment effect, i.e., the appearance of increasing dystrophin expression

with time, simply by having a lower threshold for calling fibers “positive” at later time points in the study.

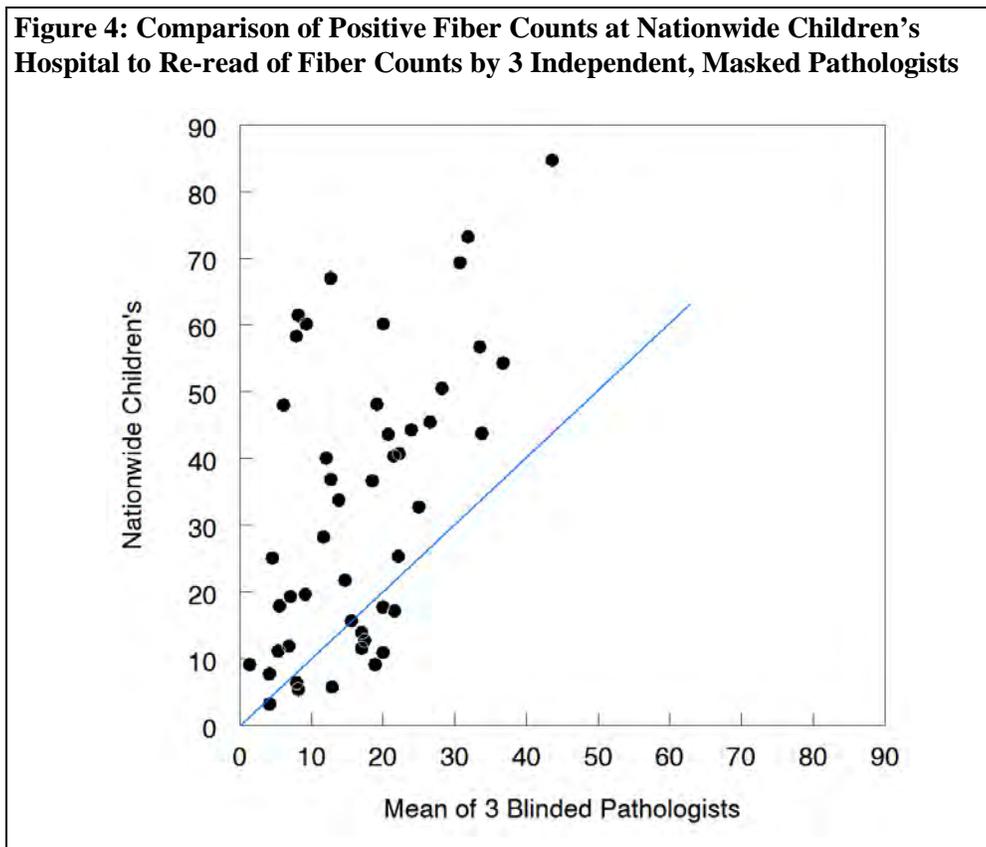
Having uncovered numerous technical and operational shortcomings in Columbus, our team worked collaboratively with the applicant to develop improved methods for a reassessment of the stored images. We suggested a re-read of all images by 3 independent masked readers, such that blinding could be assured and inter- and intra-observer variability could be characterized. We also suggested the use of better equipment, specifically, high-quality light-emitting diode (LED) computer monitors, in darkened rooms.

The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen at Week 24 (dashed red and black lines), there was no response between Weeks 24 and 48.



This re-analysis, along with the study published in 2013,² provides an instructive example of an investigation with extraordinary results that could not be verified. The publication, now known to be misleading, should probably be retracted by its authors.

Figure 4 shows the correlation between the dystrophin immunohistochemistry data as read by the technician at Nationwide Children’s Hospital and the 3 blinded pathologists. Each point represents data from a single patient at a single time point (an analysis of 24 images), as read by Nationwide Children’s Hospital (y-axis) and the group of 3 blinded pathologists (x-axis). Readings from the 3 pathologists are averaged. Perfectly correlated readings would lie along the blue line of unity. In most cases, the reading from Nationwide exceeds the reading from the pathologists, i.e., above and to the left. Thus, despite less-than-optimal lighting conditions that should have favored reduced reading of positive fiber counts at Nationwide Children’s Hospital, there was a striking tendency for the reporting of higher counts at that institution.

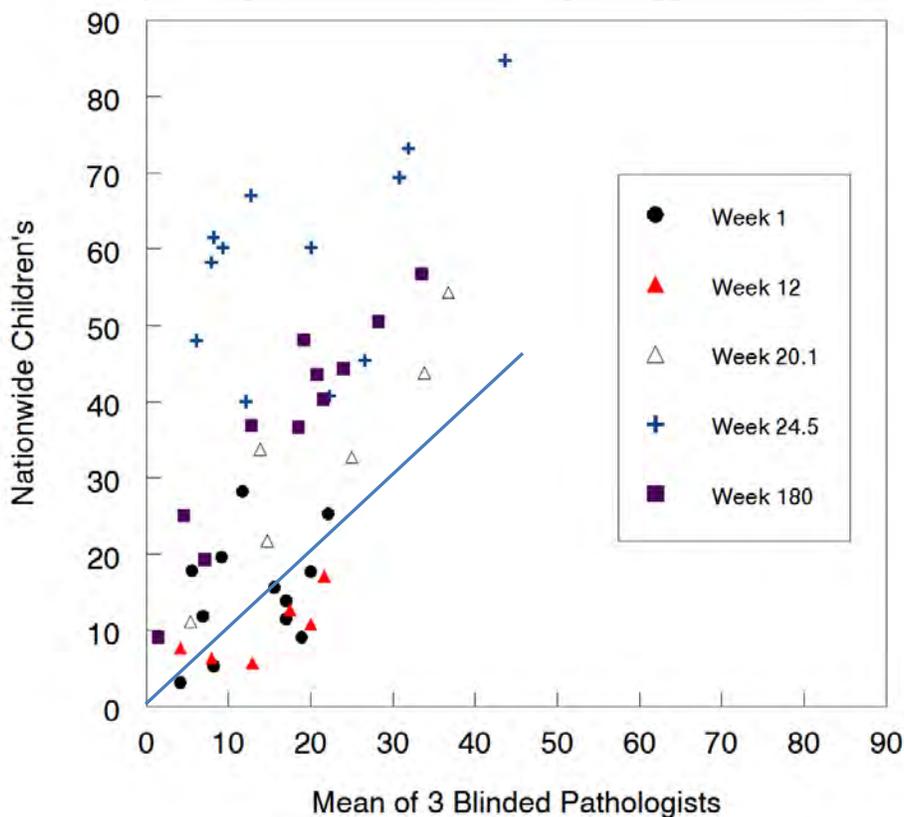


One might reasonably ask why the original readings were not reproduced by a blinded re-read. Figure 5 shows the same scatterplot between readings by Nationwide Children’s Hospital and the 3 blinded pathologists. In this display, however, readings from samples obtained at the disparate time points are shown with unique markers.

It is striking that the deviations between the readings of Nationwide and the re-read by the blinded pathologists differ substantially by study time point. Thus, at Week 1 (●) and Week 12 (▲), time points before increased dystrophin production would be expected, there is reasonable agreement between Nationwide and the pathologists, i.e., the points lie close to the blue line. In contrast, for the Week 24.5 time point (+), readings from Nationwide Children’s Hospital are much higher than those of the 3 pathologists, suggesting that blinding to sequence (i.e., time

point) was not achieved. At the time the Week 180 samples were read at Nationwide Children's Hospital, the technician was aware that the images would be re-read by 3 pathologists, which could explain why there is less exaggeration (i.e., the Week 180 readings are closer to the blue line of unity than the Week 24.5 readings).

Figure 5: Comparison of Positive Fiber Counts at Nationwide Children's Hospital to Re-read of Fiber Counts by 3 Independent, Masked Pathologists: Apparent Interaction with Time



Week 180 Data

As noted by the review team, the extension phase of the study (Study 202) has continued through the present. Eleven (11) of the 12 patients consented to undergo a fourth skeletal muscle biopsy at Week 180 (3.5 years), and these samples were analyzed using immunohistochemistry.

Prior to the analysis of the Week 180 samples, however, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Their aim was to compare the Week 180 dystrophin level to baseline for each patient. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these with samples from 6 untreated external DMD patients, all to be compared to the Study 201/202 patients at Week 180. Images were read by the same 3 pathologists, masked to treatment group.

For this analyses, the applicant claims a remarkable increase in dystrophin staining: the 9 baseline samples (including samples from 3 patients in Study 201/202 and 6 external controls) showed a mean percent positive fiber count of $1.1 \pm 1.3\%$ (mean \pm SD), whereas the Week 180 samples showed a mean percent positive fiber count of $17.4 \pm 10.0\%$. I will note that FDA made no attempt to inspect or oversee the new immunohistochemistry methods.

Given that the original baseline percent positive fiber count for patients from Study 201/202 was $13.0 \pm 6.2\%$, it would be important to understand why the results from a new immunohistochemistry protocol provided results more than an order of magnitude lower ($1.1 \pm 1.3\%$).

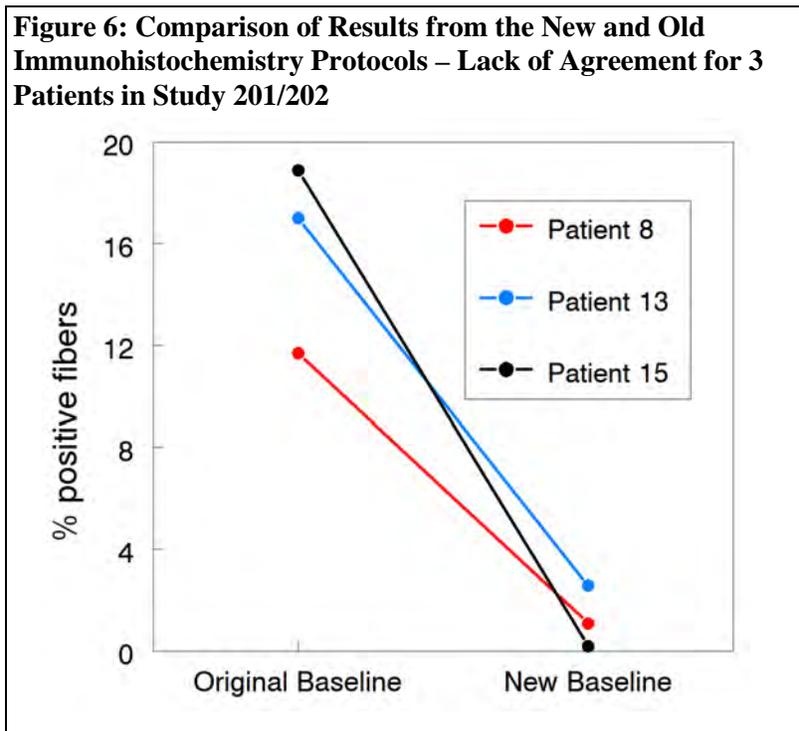
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue for separate immunohistochemistry analyses using both the old and new methods. Figure 6 shows how the two methods compare. These are essentially replicate analyses of a single tissue sample using the two methods.

There is an inexplicable difference of more than an order of magnitude between results using the new and old immunohistochemistry protocols. These marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

Commentary:

The review team provided much thoughtful discussion regarding the relative merit of immunohistochemistry for the quantitative assessment of dystrophin in skeletal muscle. My view is that such analyses, if properly blinded and controlled, can yield semi-quantitative information that could show differences in dystrophin production, e.g., 50% is more than 25%, although the method does not allow correlation of particular values of "percent positive" fiber counts with quantitative measures of muscle protein. Moreover, comparisons of fiber counts across centers, across experiments, or, for that matter, across staining or reading runs within a single laboratory, do not seem likely to be informative.



Recognizing that Study 201/202 was a small exploratory phase 1/2 study that was not powered to show a small change in dystrophin, the study provides no evidence of increased dystrophin production by immunohistochemistry.

It is unfortunate that the original readings from Nationwide Children's Hospital, purporting to show a marked effect of eteplirsen on dystrophin-positive fiber counts – counts now known to be unreliable – led to the perception that the drug produces large amounts of dystrophin. These results fueled the public perception that eteplirsen is highly effective as well as the DMD community's reluctance to participate in placebo-controlled trials. Only recently, an unauthored report in the Wall Street Journal stated: "The trial turned up evidence that eteplirsen makes good on pumping out dystrophin, a feat no treatment has managed."⁴ Presumably this misperception has been carried over from the initial 2013 reports.

B. Western blot

1) Data analyzed prior to the PDUFA goal date

A second, more important line of evidence regarding dystrophin production is Western blot, a standard, widely-used, analytical technique to assess levels of protein in biological tissues. Western blot was used to quantify dystrophin protein directly, and the methods are described by others.

For a variety of reasons discussed by Dr. Rao, the Western blot analyses originally conducted by the applicant were technically unsatisfactory. The Western blots from the first 3 time points had oversaturated bands, lacked appropriate controls, and were essentially uninterpretable. After conducting a site visit to the Columbus OH laboratory, FDA rendered advice to the applicant with the goal of improving technical aspects of the assay for future use.

The applicant amended the study protocol to allow for an additional skeletal muscle biopsy at Week 180 (3.5 years), potentially enabling pre- to post-treatment comparisons of Becker-type dystrophin after prolonged eteplirsen treatment. As noted above, 11 of the 12 patients in Study 201/202 consented to undergo a fourth skeletal muscle biopsy at Week 180. Of note, the baseline samples had been obtained from biceps muscle, whereas the Week 180 samples were obtained from deltoid muscle.

Two blocks were prepared from each patient sample. Sections from both blocks were pooled during homogenization for lysate preparation, and Western blots were run in duplicate.

The individual (anonymized) values for the Western blot analysis are shown in Table 3. As reported by the review team, the analysis for 11 of the 12 original patients showed a mean dystrophin value of 0.93% ± 0.84% of normal (mean ± standard deviation) after 3 to 3.5 years of eteplirsen treatment (3 years in patients initially randomized to placebo; 3.5 years in the other patients). Mean values were virtually the same for the lower (30 mg/kg/week) and higher (50 mg/kg/week) dose groups; there is no suggestion of a dose-response.

⁴ A Legal Test for the FDA: Black letter law dictates approval for a muscular dystrophy drug; Wall Street Journal, May 9, 2016.

Of note, the Western blot values are quite variable, both between patients and between duplicate runs *within* patients (i.e., repeatability; intra-assay precision), Table 3.

Mean values ranged from a maximum of 2.47% in Patient J, to near-zero in Patient H, and to zero in 2 patients (E and G). For some patients, there were considerable discrepancies between duplicate runs (the intra-assay difference was >0.5% in Patients B, C, D, and J). Aside from patients with zero or near-zero dystrophin, only 3 patients showed reasonable intra-assay agreement: Patients F, L, and K.

Given that these numbers represent duplicate runs from tissue homogenates, intra-assay differences suggest limited precision/reproducibility of the method, heterogeneity of the samples, or both.

Table 3: Individual Week 180 Western Blot Analyses – Study 201/202

Subject	Dose	Western blot				Group Mean ± SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)	
L	30 mg/kg	0.58	0.46	0.52	0.52	
K	30 mg/kg	1.45	1.78	1.62	1.62	
J	30 mg/kg	2.83	2.11	2.47	2.47	
H	30 mg/kg	0.02*	0.28	0.15	0.14	
G	Placebo to 30 mg/kg	0.17*	0.15*	0.16	0	
F	Placebo to 30 mg/kg	0.93	1.02	0.98	0.98	0.96 ± 0.95
E	50 mg/kg	0.19*	0.16*	0.18	0	
D	50 mg/kg	0.75	0.24*	0.50	0.38	
C	50 mg/kg	1.22	0.69	0.96	0.96	
B	50 mg/kg	2.43	1.67	2.05	2.05	
A	Placebo to 50 mg/kg		1.15	1.15	1.15	0.91 ± 0.79

* below limit of quantitation

Change in Dystrophin with Treatment:

The critical question, of course, is whether the value of 0.93% is meaningfully greater than the value at baseline, or even meaningfully greater than zero. Assuming that one considers this value greater than zero, the baseline pre-treatment levels of dystrophin in these 11 patients are critical in determining whether eteplirsen was responsible for the dystrophin detected at Week 180.

Unfortunately, adequate pre-treatment tissue samples were available for only 3 of these 11 patients. Thus, the applicant supplemented these data with muscle biopsies from 6 untreated patients with DMD amenable to exon 51 skipping who were external to the study.

Whereas the Week 180 samples were obtained from deltoid muscle, 8 of 9 of the controls were obtained from biceps muscle (the other one was obtained from deltoid). As noted above, the non-clinical review team found "...wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is

warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients.” Use of disparate muscle groups between patients in Study 201/202 and controls was, obviously, ill advised. The finding of a difference between patients in Study 201/202 and the external controls could simply represent a difference between muscles.

FDA’s advice to the applicant (March 30, 2015) is still germane: "The control biopsy tissue that you propose to use is from a number of different muscle groups, such that differences that may exist in dystrophin expression among muscle groups may affect your results. However, in the context of other major sources of variability among biopsies (including both intra- and inter-individual differences even within the same muscle group), it appears reasonable for you to proceed with these controls, with the understanding that dystrophin changes would need to be robust to be interpretable as a drug effect."

Averaging Western blot data from pre-treatment biopsies of the 2 patients from Study 201/201 and the external treatment-naïve patients, the applicant reported a baseline dystrophin value of 0.08% ± 0.13% (mean ± standard deviation). Obviously, all but 2 of these controls are external, such that the comparison to the treated patients in Study 201/202 is non-randomized and indirect.

Table 4: Individual Untreated DMD Control Samples, Western Blot Analysis (% Normal Dystrophin)

Study; Subject	Dose	Western blot				Group Mean ± SD	All Mean ± SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)		
201/202; X	0	0.05*	0.07*	0.06*	0	0 ± 0	0.08 ± 0.13
201/202; A	0	0.19*	0.08*	0.14*	0		
201/202; B	0	0.13*	0.07*	0.10*	0		
external; A	0	0.12*	0.14*	0.13*	0	0.12 ± 0.15	
external; B	0	0.03*	0.12*	0.08*	0		
external; C	0	0.37	failed	0.37	0.37		
external; D	0	0.04*	0.30	0.17*	0.15		
external; E	0	0.20*	failed	0.20*	0		
external; F	0	0.40	0.09*	0.25*	0.20		

* below limit of quantitation

In determining whether there is substantial evidence that eteplirsen produced dystrophin in the patients in Study 201/202, the critical questions are whether these values, near the lower limit of quantification of the assay, are actually interpretable, and whether the comparison between these subjects and a predominantly external group of untreated patients is valid.

The review team has pointed out important limitations with respect to comparability of the Western blot results from the untreated controls, summarized below:

- Biopsies from controls were obtained from biceps, whereas Week 180 biopsies from eteplirsen-treated patients were obtained from deltoid. There is some evidence that dystrophin concentrations differ by muscle group, and the study does not account for this possibility. Because the study is not well controlled, the difference between these groups of patients cannot be attributed to a drug effect.
- Two-thirds (6 of 9) of the control patients were from Study 301, and were external to study 201/202. There is no way to know how these particular patients were selected for the purpose of this comparison.
- Degradation of dystrophin or loss of immunoreactivity might occur during prolonged storage of tissue samples. If so, it could have affected the baseline samples from the 3 patients in Study 201/202, which were frozen for over 3 years prior to analysis. Note that the data are consistent with loss in immunoreactivity over time (Table 4). The per-protocol values for all 3 patients from Study 201/202 whose samples were stored for 3 years are 0 (top), whereas 3 of 6 of the samples from the external controls (bottom) are greater than zero. Although the numbers of samples are small and the comparison is non-randomized, the data nevertheless support the concept that immunoreactive dystrophin decreases during storage.

For these reasons, the review team questioned the comparability of these two groups of patients, and I agree. Having compared samples from different muscle groups in independent groups of patients, the study was not adequate and well controlled; therefore, the validity of the comparison is uncertain. The data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Having heard arguments and opinions from both the applicant and the review team, the Advisory Committee, despite extraordinary public activism and pressure to vote favorably, voted 7 to 6 that the applicant had 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. Moreover, 2 of the Committee members who voted “yes” were patient representatives.

Correlation between the applicant’s two methods to assess dystrophin

The discussion of the Week 180 dystrophin analyses would not be complete without a comparison of the results of the two complementary methods used by the applicant. Of note, the improved immunohistochemistry analyses and Western blot analyses were performed on *the same blocks of tissue*, and one should expect a reasonable correlation between the two methods if in fact the data are reliable.

Of note, there is a striking lack of correlation between these two methods of dystrophin assessment (Figure 7). It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, whether the Western blot methods are inaccurate, or whether both methods are inaccurate. My view is that it is not possible to render a positive regulatory decision on the basis of unreliable data from these 11 patients. Internal consistency is lacking.

2) Data analyzed after the PDUFA goal date

As noted above, as the May 26, 2016 goal date was approaching, OND and CDER could not reach agreement on the regulatory action for this NDA.

In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301 [PROMOVI]). These samples were originally planned to be analyzed at the end of the study;

however, we requested an interim analyses of a subset of samples. As described by Drs. Rao, Farkas, and Bastings, Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples had been obtained at baseline (prior to treatment) and at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

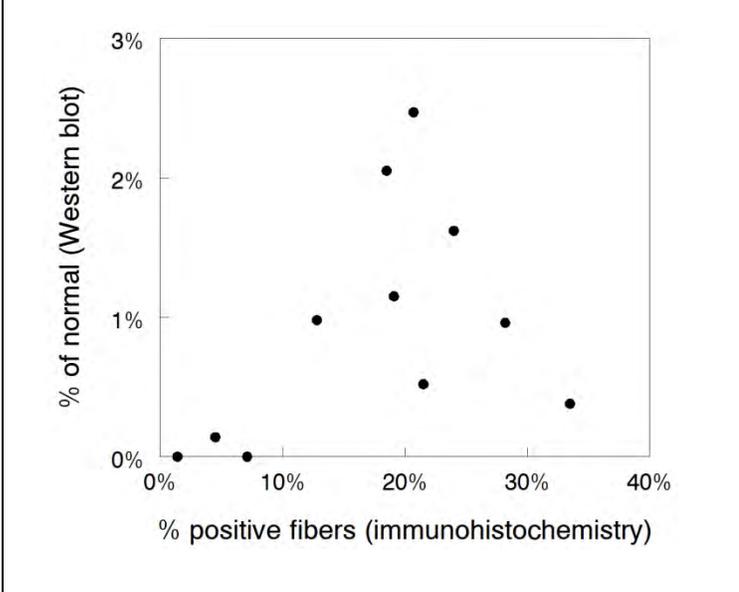
The age of these 13 patients ranged from 7 to 13 years. Paired pre- and post-treatment samples were run in side-by-side lanes on the gels, and each gel was run in duplicate. A muscle sample from a healthy 14 year-old boy with no pathologic diagnosis served as the reference sample; values from the DMD patients were reported as percent of normal.

Dr. Ashutosh Rao from the Office of Biotechnology Products reviewed the methodology and the technical reliability of the Western blot assay. Dr. Rao also conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) as the analyses were being run. Xiang Ling, Ph.D., from the Office of Biostatistics, performed the statistical review on the data.

According to the protocol, acceptance of the result from each gel was contingent on two factors: 1) the R^2 value for the linearity of the standard curve of the normal control had to be > 0.9 ; and 2) the dystrophin band for the negative control DMD sample on the gel had to have a density lower than the lowest sample of the standard curve (0.25%). Samples that did not meet both criteria were deemed 'failed' and were not considered in the analyses. As it turned out, 22 of the 52 gels (42%) failed, such that many of the values represent single readings rather than the average of two. There was one patient for whom none of the values met acceptance criteria. Thus, the applicant reported pre- and post-treatment data for 12 of the 13 patients.

The applicant used 3 methods to consider values below the 0.25% lower limit of quantification: 1) consider such values to be zero; 2) analyze such values as actually reported; and 3) consider such values to be 0.24%.

Figure 7: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



The review team believes the most appropriate analysis is the second: analysis of all values as reported, but the results were similar for all 3 methods.

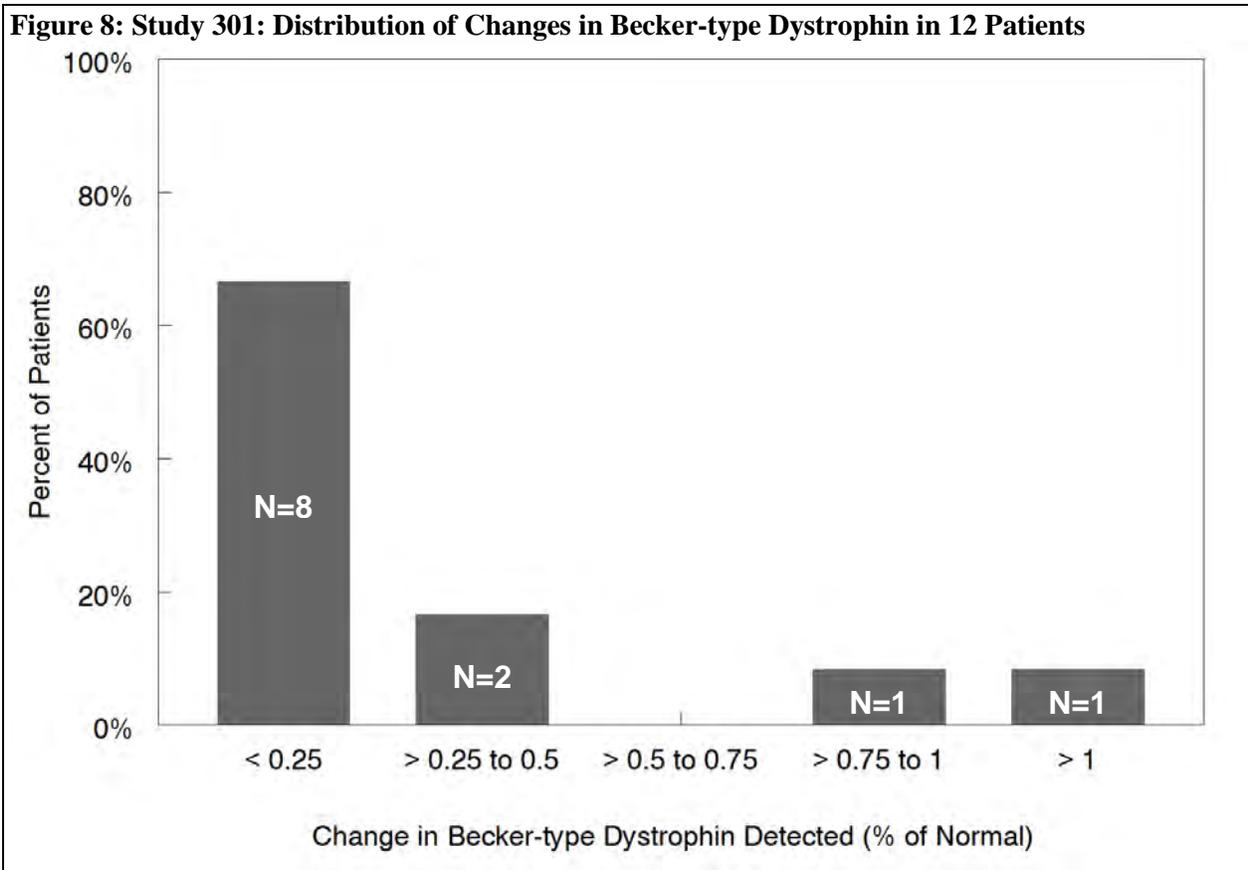
Reporting values below the limit of quantification as 0, pre- and post-treatment values are $0.06\% \pm 0.14\%$ and $0.38\% \pm 0.50\%$, respectively (mean \pm standard deviation), $p < 0.05$. For the 'as reported' analysis, pre- and post-treatment values are $0.16\% \pm 0.12\%$ and $0.44\% \pm 0.43\%$, respectively, $p < 0.05$. Reporting all values below the limit of quantification as 0.24%, pre- and post-treatment values are $0.26\% \pm 0.05\%$ and $0.48\% \pm 0.41\%$, respectively, $p < 0.05$. Individual data for the 'as reported' analysis are shown in Table 5, adapted from listing 1.1 of the applicant's "Preliminary Report: Western Blot Interim Analysis of Novel Dystrophin Expression in Muscle Biopsy Samples from Week 48 of the Clinical Study 4658-301," submitted June 27, 2016.

Irrespective of the method used to express data below the limit of quantification, the mean change is similar, ranging from 0.22% to 0.32% of normal, a treatment effect of approximately 2 to 3 parts per thousand.

Table 5: Study 301: Pre- and Post-treatment Values of Becker-Type Dystrophin

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.14	1.33
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08	1.17	
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	0.24	1.33
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17	1.57	
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12	0.12	
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31	0.47	
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09	0.09	
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34	0.21	
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25			fail	0.04	0.17	
		pass	0.17					pass	0.17		
	Week 48	fail	0.22	0.42				fail	0.22	0.42	
		pass	0.42					pass	0.42		

The distribution of these changes is shown graphically in Figure 8. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a treatment effect greater than 1%.



Commentary: Study 301 was a baseline-controlled study, where each patient served as his own control: pre- and post-treatment biopsies were obtained from the same muscle and Western blot analyses were run concurrently. An FDA inspection team observed the performance of the assays and considers the results to be reliable. Thus, unlike the data obtained from Study 201/202, the Study 301 data are considered by the review team to have been generated from an adequate and well controlled study. Study 301 provides substantial evidence of an effect of the surrogate endpoint – Becker-type dystrophin.

The critical question is whether the quantity of dystrophin produced here – a mean of 2 to 3 parts per thousand – is reasonably likely to predict clinical benefit.

With levels of Becker-type dystrophin higher in Study 201/202 (at Week 180) than in Study 301 (at Week 48), the applicant speculates that there is greater dystrophin accumulation with longer durations of treatment. These differences, however, could also be due to cross-laboratory methodological differences or play of chance; therefore, such an interpretation is highly speculative.

The Question of “Reasonably Likely to Predict Clinical Benefit”

As discussed above, the accelerated approval of eteplirsen hinges on: 1) whether Becker-type dystrophin is an appropriate surrogate endpoint for the disease; 2) whether there is substantial evidence that eteplirsen produces Becker-type dystrophin in skeletal muscle, and 3) whether such dystrophin produced is reasonably likely to predict clinical benefit, i.e., whether it is functional, and whether the quantity produced is adequate.

1. Is dystrophin an appropriate surrogate endpoint for Duchenne muscular dystrophy?

The review team believes that dystrophin is on the causal pathway of the disease, and there is no debate about the appropriateness of dystrophin as a surrogate endpoint for Duchenne muscular dystrophy.

2. Is there substantial evidence that eteplirsen produces dystrophin in skeletal muscle?

Prior to receiving the new Western blot data from Study 301 on June 27, 2016, the review team did not believe that substantial evidence from adequate and well controlled trials had been submitted to support an accelerated approval.

Study 201/202: Immunohistochemistry analyses were performed to assess and compare percent dystrophin-positive fibers at various time points before and during treatment. This is a standard technique that has been used by many laboratories for decades to assess dystrophin levels in DMD and Becker’s patients. Importantly, the analysis showed no evidence of dystrophin production through 48 weeks of treatment with eteplirsen. This information is particularly germane, because, unlike the Western blot analyses from Study 201/202, the immunohistochemistry analyses are adequately controlled. The lack of a positive finding from the blinded re-read of the immunohistochemistry data with proper controls undercuts the evidence of dystrophin production from Western blot analyses.

The applicant supplemented these data with new analyses from Week 180 that purport to show a remarkable increase in dystrophin from pre-treatment levels. Unfortunately, an altered immunostaining protocol was used, and there was an inexplicable difference of more than a log between results from the new and old protocols, rendering interpretation impossible.

The Western blot data from Study 201/202 were largely externally controlled, and there were questions with respect to the proper selection of control patients, differences in the specific muscles analyzed, and concerns regarding the possible degradation of immunoreactive dystrophin in tissue samples that might occur during long-term storage and lead to a false-positive result. Importantly, ignoring the baseline data and focusing only on the Week 180 samples, there is a striking lack of correlation between the immunohistochemistry data and the Western blot data, i.e., there is no internal consistency. Thus, these data provide no basis to believe that the study was adequate and well controlled.

Study 301: The new data submitted on June 27, 2016 were obtained from an adequate and well controlled study. This baseline-controlled study shows a statistically significant increase in Becker-type dystrophin with treatment, the surrogate endpoint. Thus, there are now data showing Becker-type dystrophin production, albeit at a small level, from one adequate and well controlled trial (Study 301), with inconclusive data from Study 201/202.

The question of “reasonably likely” is, therefore, an issue of the quantity of protein produced. As noted above, Study 301 showed a treatment effect of 2 to 3 parts per thousand in Becker-type dystrophin after 48 weeks. Study 201/202, although not adequate and well controlled, nevertheless suggested a treatment effect of 8 to 9 parts per thousand after 3.5 years.

3. Is the dystrophin that was produced reasonably likely to predict clinical benefit, i.e., is it functional, and is the quantity adequate?

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Function is therefore a matter of judgment for which regulatory flexibility can be extended. The review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as in the Becker form of the disease. Although there can be no certainty on this point, the uncertainty is small relative to the uncertainty regarding the adequacy of the quantity, and so function is less germane to the question of “reasonably likely.” In short, it is the *quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.*

It must be stated that the minimum level of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown. The raw data are shown in Figure 9, but this is an area where we must consider what is known about the disease and apply medical judgment.

There are two ways to consider the quantity of Becker-type dystrophin produced: as a binary responder analysis, and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

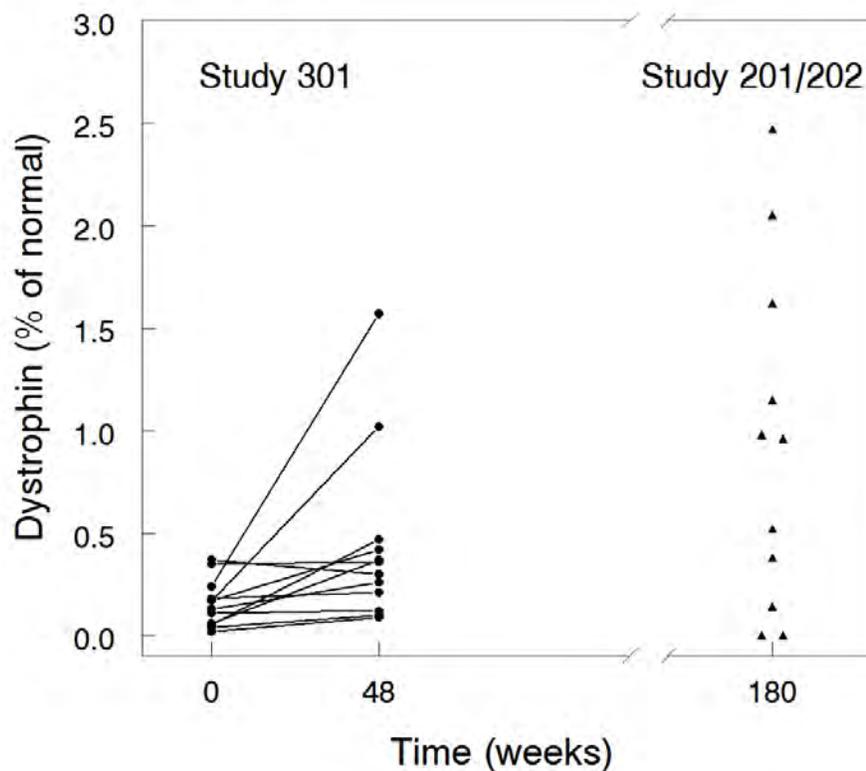
The problem with a responder analysis is that there is no rational basis upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Drs. Farkas and Bastings have tried to provide a framework to help put these small increases into perspective. The applicant’s data show that dystrophin levels in treatment-naïve DMD patients range from 0 to approximately 0.4% by Western blot; the applicant has not detected values > 0.4% in treatment-naïve patients.

DMD experts, including those involved with the development of eteplirsen, have stated that levels < 3% are generally associated with the typical DMD phenotype, and no patient has been found to have or produce a level of Becker-type dystrophin > 3% in response to treatment.

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have focused on publications from a number of laboratories that attempt to relate particular levels of dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Some have also cited non-clinical data to relate dystrophin levels to maintenance of physical function. It is important to recognize, however, that many methodological factors affect the results of these assays, and comparison of values across various laboratories could lead to erroneous conclusions.

Figure 9: Studies 301 and 201/202: Expression of Becker-type Dystrophin by Western Blot



Van den Bergen *et al* studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker muscular dystrophy (van den Bergen JC, et al. *J Neurol Neurosurg Psychiatry* 2014;85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their patients with dystrophin levels <10% showed low muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Chamberlain, who stated at the open public session at the advisory committee meeting that very low levels of dystrophin may be beneficial, discussed in a published paper (*Basic Appl Myol.* 7 [3&4]: 251, 1997) that “...a majority of fibers must accumulate approximately 20% of wild-type levels of dystrophin for a significant correction of the muscle pathology,” a view that seemingly contradicts the comments he made at the advisory committee meeting.

Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. Variability was particularly pronounced with low levels of dystrophin.

During their presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, stated:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: official transcript of the meeting; underlining for emphasis.)

It appears, therefore, that reproducibility of assays among academic centers has not been established, such that it would not be feasible to compare an increase in Becker-type dystrophin of 0.2 to 0.3% (or even far greater increases) with dystrophin values cited in the literature for other mutations/patient populations, assessed by other laboratories.

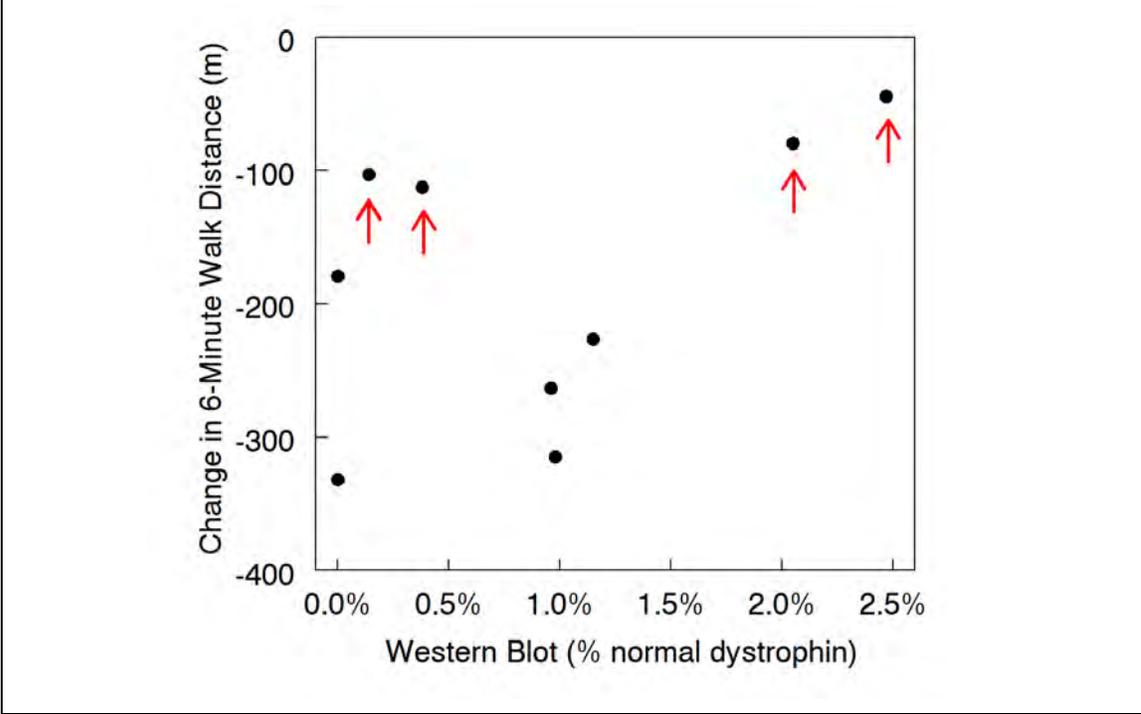
Do the clinical data bolster the question of “reasonably likely?”

The applicant collected data on both dystrophin production and physical performance in Study 201/202. Such data have the potential to support the concept that the dystrophin level predicts clinical response, and would support the ‘reasonably likely’ premise. Despite detailed testimonials from patients in Study 201/202 claiming improvements in clinical performance, the Division concluded, on the basis of the data presented in the NDA, that no patient in Study 201/202 clearly deviated from the natural history of the disease. They reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Dr. Bastings opines that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

Within Study 201/202, it is also reasonable to consider the correlation between the quantity of dystrophin detected and maintenance of physical function in individual patients. The presence of a correlation would help support the “reasonably likely” question.

For the 9 patients who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, Figure 10 shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years. For the 4 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study, but 2 had levels that were close to zero. Importantly, therefore, these data do not show a quantitative correlation between the surrogate endpoint deemed reasonably likely to predict clinical benefit, i.e., Becker-type dystrophin levels, and the clinical benefit, i.e., maintenance of walking velocity. In Dr. Bastings’ memorandum, he provides careful documentation of the trajectories of physical performance for each patient, comparing their changes in performance to the quantity of dystrophin detected. After careful consideration, he finds no correlation whatsoever.

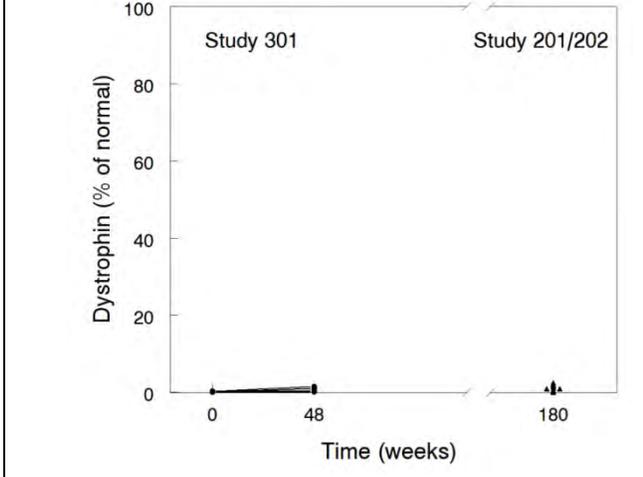
Figure 10: Study 201/202 – Lack of Correlation between Quantity of Dystrophin Detected and Preservation of Physical Function (6-Minute Walk Distance)



Although it should be obvious that changes on the order of a percent or two are small, it is nevertheless worthwhile to view these data at full scale to gain perspective (Figure 11). The figure is identical to Figure 9, except for the scale on the y-axis.

If dystrophin were simply an enzyme responsible for biochemical activity in myocytes, one could posit that a very small quantity of the protein could exert a substantial treatment effect, especially because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury from stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. Finally, we must recognize receiving a treatment that increases dystrophin by 0.3% is not that same as being born with 0.3% more dystrophin.

Figure 11: Studies 301 and 201/202: Expression of Becker-type Dystrophin by Western Blot (full scale)



3. Dose-response

Although the issue is somewhat peripheral to the “reasonably likely” question, the presence of a dose-response in Study 201/202 would have provided supportive evidence that the dystrophin that was detected was produced by eteplirsen. A dose-response was not evident, although one could reasonably argue that the trial was very small and that the difference between 30 and 50 mg/kg/week was unimportant.

In a monkey study conducted to assess the pharmacodynamic effects of eteplirsen, a 1-log increase in dose (from 4 to 40 mg/kg) caused minimal increase in exon 51 splicing as detected by PCR (Section 4, Table 1). However, with a 2-log increase in dose (from 4 to 320 mg/kg), there was a log increase in exon 51 splicing. As noted in Section 4 of this memorandum, it is possible that much higher doses of eteplirsen could have a substantially greater effect, which might translate to clinical benefit.

Advisory Committee

The Advisory Committee was asked to discuss: a) the strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients relative to their baseline, and b) the 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. (Of note, the data from Study 301 were not known/available to the Advisory Committee.)

Although the Committee failed to reach consensus on these questions, the discussion, summarized below, is of interest.

With respect to production of dystrophin, about half of the committee members found evidence that eteplirsen increased the amount of dystrophin produced in skeletal muscles. 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 (Figure 10), and one cited concerns about the lack of a dose-response (Table 3).

Only four Committee members had explicit comments with respect to the clinical meaningfulness of the amount of dystrophin detected in treated patients, and their opinions were split. One member 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 felt strongly 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 there is no basis to determine the quantity of dystrophin that 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 in the study, the amount was not clinically meaningful, based on the lack of correlation between dystrophin levels and clinical results (Figure 10).

The Committee voted on whether the applicant had 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.

Ultimately, 7 members voted “no” and 6 voted “yes,” after one member changed his vote from “no” to “yes.” In explaining their “no” votes, 5 committee members opined that the studies were not adequate and well controlled; they 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 6 “Yes” votes included the consumer representative and 2 patient representatives. These individuals 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. Two members who voted “No” stated that their vote was justified by the way the question was phrased, but that the patient testimonies suggested the drug works.

Is There a Basis for a Conventional Approval Based on Clinical Data?

The clinical data have been well described by the review team. The development program consisted of one trial (Study 201/202) with a relatively short (24-week) placebo-controlled portion (Study 201) followed by a long-term extension study (Study 202). Although the applicant submitted biopsy data from the ongoing Study 301, no clinical data have been submitted from that study.

As noted above, for Study 201, patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2) and followed for 4 additional weeks. The trial was extended to an open-label phase (Study 202), where all 12 patients continued to receive eteplirsen without interruption, although investigators and patients remained blinded to dose.

The 1^o endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry, but there were numerous exploratory endpoints.

When the data from Study 201 were originally analyzed, the applicant found that eteplirsen caused a striking and unprecedented increase in dystrophin production, based on the reading of the immunohistochemistry data at Nationwide Children’s Hospital, with supportive data from Western blot analyses.

The clinical data, too, were interpreted as positive. As discussed by the review team, 2 patients in the 30 mg/kg/week treatment group became unable to ambulate soon after the trial began, and there were no significant differences in 6-minute walk distance among the groups. Despite clearly negative results, the applicant performed a *post hoc* analysis that omitted the 2 patients in the eteplirsen group who became unable to ambulate. They represented these results as positive, and publically promoted both the immunohistochemical dystrophin results and the 6-minute walk data as positive (see clinical review).

Although FDA would later determine that the analyses underlying these data were not valid, the publicity from the paper² and Sarepta’s press release³ raised unrealistic expectations of efficacy

in the DMD community. It was these perceptions that led the applicant to conclude that a second placebo-controlled study would not be feasible.

FDA strongly suggested a second, larger, adequately-powered, placebo-controlled trial, but the applicant was reluctant to run such a trial, in part because their supply of drug was limited, and in part because of their insistence that the DMD community would not agree to participate in a trial where there was a chance of receiving placebo. Faced with the applicant's unwillingness to conduct a second placebo-controlled trial, FDA agreed to an externally-controlled trial: a comparison between patients in the ongoing Study 202 and patients in an external control group. The Division expressed strong concern, however, with respect to the interpretability of such a trial with 6-minute walk distance as the endpoint, given that physical performance is not a "hard" endpoint, but can be influenced by motivation and other factors. Citing FDA Guidance,⁵ the Division noted that the treatment effect would have to be dramatic for the results from an externally-controlled study to be interpretable. Details of the interactions between FDA and Sarepta are well documented by the review team.

International guidelines, adopted by the FDA as guidance, stress caution with respect to the interpretation of data from externally-controlled trials. As noted in the International Conference on Harmonization (ICH) E10 Guideline,⁵ blinding and randomization, used to decrease bias in randomized controlled trials, are not utilized in externally-controlled trials; the inability to control bias is a critical limitation of externally controlled trials. Groups can be dissimilar with respect to a wide variety of factors that could influence outcome – factors that are both known and measurable as well as factors that are unknown. As explained by Dr. Robert Temple at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, it has been well documented that untreated historical-control groups tend to have worse outcomes than apparently similarly chosen control groups of randomized studies, possibly reflecting a selection bias.

The ICH E10 Guideline explains: "A consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials. The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." In essence, in order to be interpretable, the finding of a difference between groups should be large – so large that the difference is patently obvious without the need to rely on inferential statistics.

Having heard FDA's concerns regarding the potential difficulty in interpreting an externally-controlled trial, the applicant nevertheless obtained access to individual data from patients with DMD from Professor Eugenio Mercuri at the Catholic University in Rome on behalf of the Italian DMD Registry database (n=97) and from Professor Nathalie Goemans at the University Hospitals in Leuven (n=89). From these 186 patients, 50 had a genotype amenable to exon skipping therapy, were using corticosteroids at baseline, had 6-minute walk data available at baseline, and were ≥ 7 years old. Among these 50 patients, 13 had a genotype amenable to

⁵ Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001

exon 51 skipping therapy. I will note that the review team has been unable to gain an understanding of how dates of inception were determined for registry patients, i.e., when patients were considered to have ‘enrolled.’

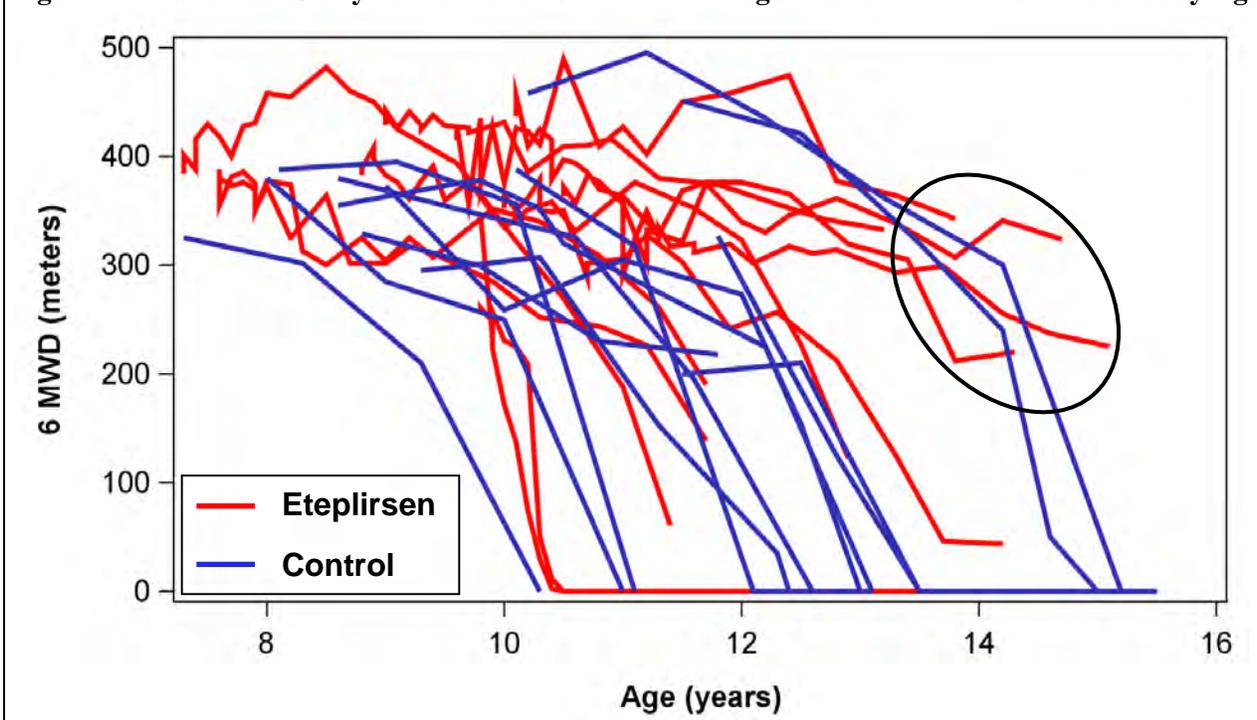
Study 202 was continued, therefore, with patients continuing to receive either 30 or 50 mg/kg/week eteplirsen. Numerous comparisons of physical function were planned between these 12 patients and the 13 patients in the external control group. Measures included 6-minute walk, rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA).

With two small groups of patients, there was no way to match patient pairs. Fortuitously, the mean ages and 6-minute walk distances were well matched at baseline, although the review team found that initial age of steroid use and baseline NSAA scores were dissimilar between groups – and both of these differences favored the eteplirsen group.

It is clear that some patients exited the registry to enroll in clinical trials. Thus, DMD patients who remained in the Italian and Belgian registries (the control group): 1) did not seek knowledge (or lacked knowledge) regarding applicable clinical trials into which they might have enrolled; 2) sought enrollment in trials but did not qualify; or 3) qualified for enrollment in a trial(s) but made a conscious decision not to participate. Obviously, such patients could differ substantially from patients in Study 201/202. The point is that there can be unknown factors beyond baseline age, weight, length of steroid use, and 6-minute walk distance that importantly affect outcomes.

The applicant presented the data by time-on-treatment, but because physical abilities change significantly with age in patients with DMD, the review team believes that the more meaningful way to display the longitudinal 6-minute walk data is by age (recognizing that both analyses have advantages and limitations, and that there is no ideal way to present these data). The 6-minute walk data are shown in Figure 12 as a function of age. The review team stresses that,

Figure 12: Patients in Study 202 vs. Patients in External Registries: 6-Minute Walk Distance by Age



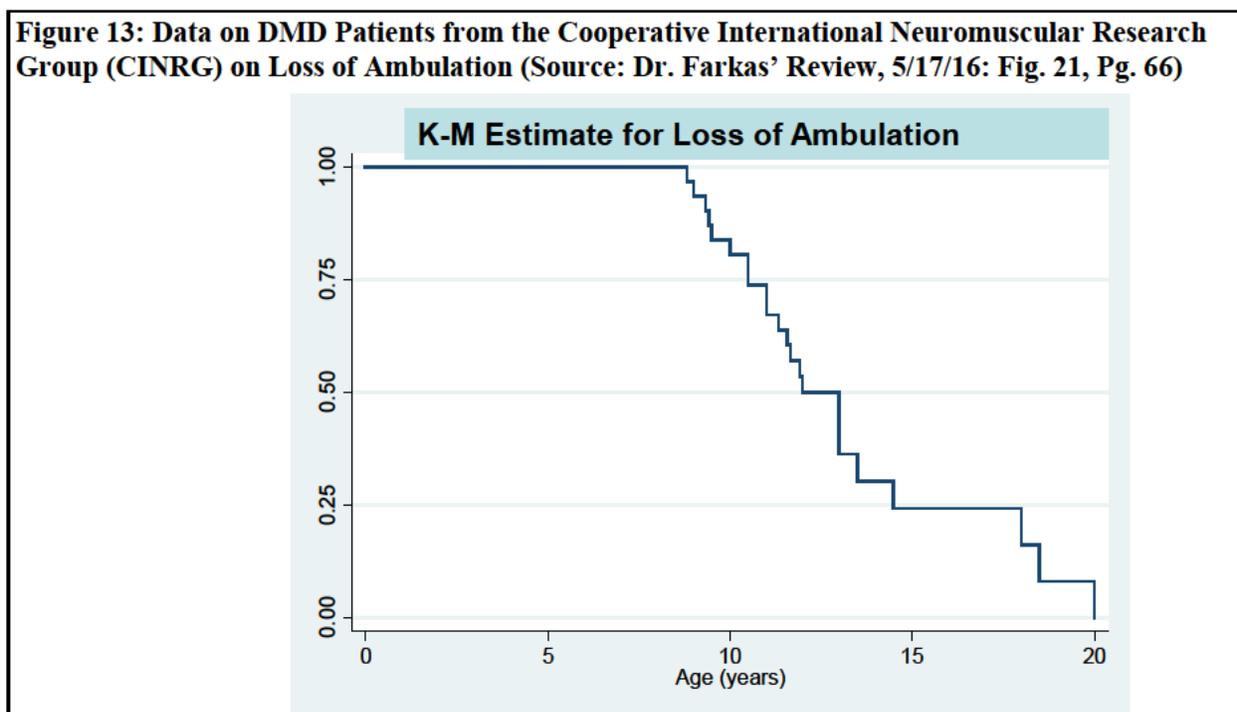
by simple visual inspection, the two groups show little difference in performance.

There are 4 patients in the eteplirsen group, ~14 to 15 years of age, who continue to retain good walking ability (inside the oval). There are 2 control patients in this age range who had been maintaining similar walking ability, but appear to have experienced a precipitous loss of ambulation between ages 14 and 15. As explained by the review team, there are concerns regarding the comparability of the assessments of these patients, and concerns about comparability of the groups in general.

The applicant's argument for accelerated approval is based on this comparison of 6-minute walk distance between the patients in Study 202 and the patients in the external control group from Italy and Belgium. The difference in 6-minute walk distance is certainly statistically significant. The problem is that the study was externally-controlled, and the statistical test was based on a non-randomized comparison.

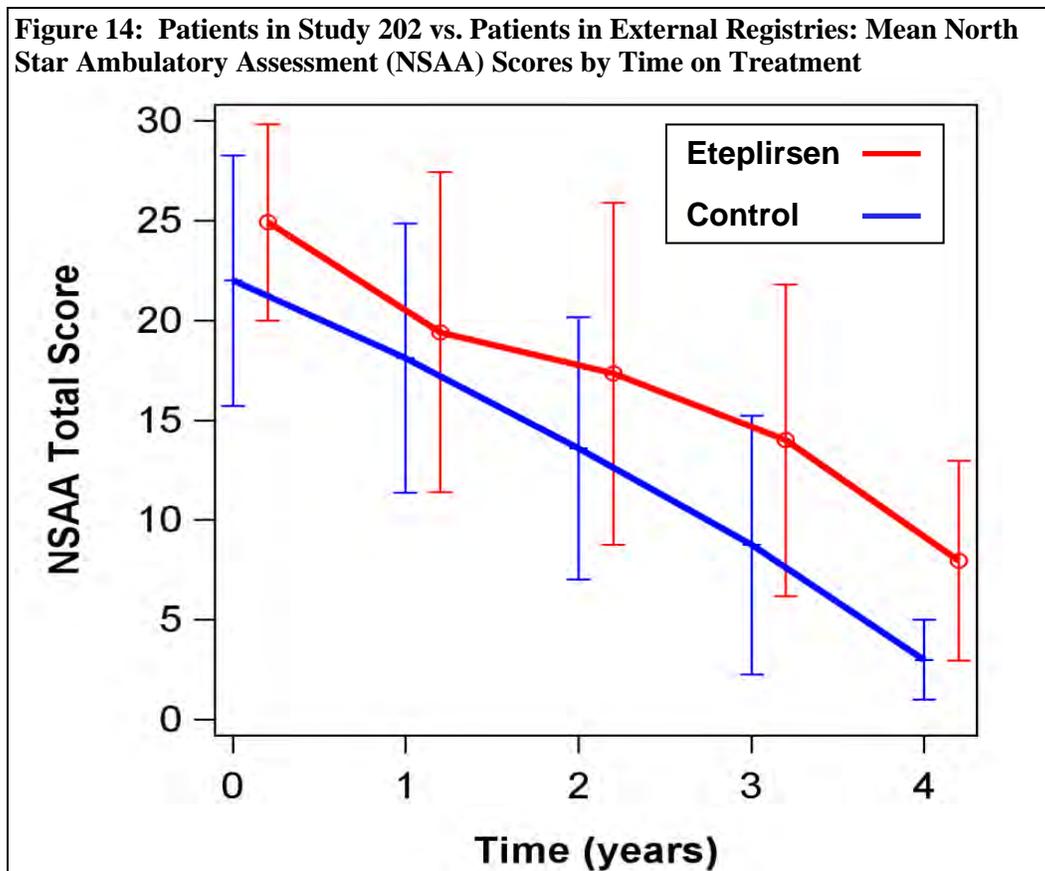
Data from the Cooperative International Neuromuscular Research Group (CINRG) provide an additional source of information on the natural history of patients with DMD. Figure 13 is a Kaplan-Meier (K-M) survival curve from CINRG showing time-to-loss of ambulation. Of note, 25% of patients remain ambulatory at age 17; their course seems quite consistent with that of patients from Study 201/202.

Figure 13: Data on DMD Patients from the Cooperative International Neuromuscular Research Group (CINRG) on Loss of Ambulation (Source: Dr. Farkas' Review, 5/17/16: Fig. 21, Pg. 66)



In summary, the review team strongly believes that patients on eteplirsen in Study 201/202 do not demonstrate a substantial treatment effect on walking velocity that clearly differentiates their course from the natural history of the disease. For a more complete description with comprehensive patient profiles, see the reviews of Drs. Breder and Farkas and the memo of Dr. Bastings.

Finally, as stressed by the review team, the data from other measures of physical function, i.e., rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA), show steady decline in the eteplirsen-treated patients that does not differ substantially from the decline in the external control group. The NSAA data are shown in Figure 14 by time on treatment (eteplirsen patients) or time since inception (registry patients). The NSAA is thought to be a comprehensive outcome measure, well reflecting the functional abilities of DMD patients. Of note, the downward trajectories of the two groups are indistinguishable (the lines are virtually parallel with equal slopes).



Patient Testimony/Advisory Committee:

In addition to the presentations made by the applicant and the review team at the April 25, 2016, Advisory Committee Meeting, there were testimonies from over 50 individuals and families, including most of the patients who were participating in Study 202. (Per email communication from (b) (4), one of the applicant’s consultants, 10 of the 12 patients testified and another patient had someone speak on his behalf.)

In addition, the applicant invited Christine McSherry, Executive Director of the Jett Foundation, to present “Patient and Caregiver Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne.”

The testimonies of these patients were quite consistent and remarkably positive: all were convinced that eteplirsen had made a substantial positive impact on their physical performance, improving numerous aspects of their lives.

It was noteworthy that a number of individuals who were in Study 201/202 reported *improvement* in physical function with eteplirsen treatment. For example, one patient stated that he had required a wheelchair at a school he had attended in the past, whereas he no longer needed a wheelchair at his present school. A video showed a boy who, prior to treatment, had some difficulty climbing up into the seat of a minivan. After receiving eteplirsen for several months, he was shown jumping up easily into the seat. In another video, a boy in the study threw a football, a tight spiral, with ease and finesse.

Many of the Committee members seemed obviously moved and deeply affected by these testimonies and videos, seemingly convinced that there was a treatment effect.

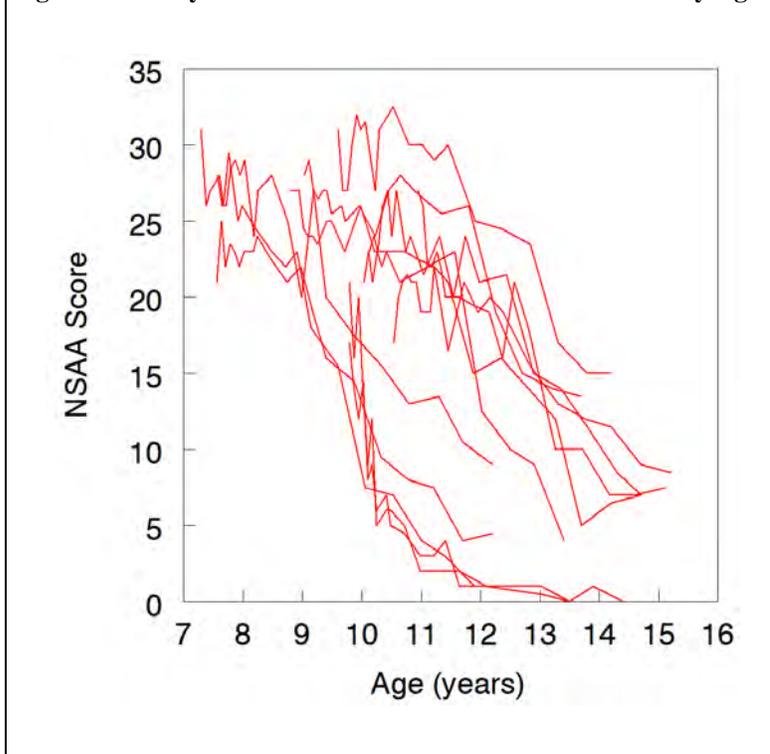
Importantly however, despite the claims of improvement made at the microphone at the Advisory Committee meeting, the review team did not find any patients in Study 201/202 with consistent improvement in physical performance as assessed by formal testing (6-minute walk, rise time, NSAA, 10-meter run). These tests have shown moderate to extreme declines in physical function for all patients (see NSAA data, Figure 15).

Thus, the review team and many on the Advisory Committee (including Benjamin Dupree, the patient representative with DMD), were unable to reconcile the patient testimonies with the data collected by the applicant: the testimonies spoke of *improvement*; the data showed *progressive worsening*.

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD.

The 7-member majority of the committee who voted "no" agreed that Study 201/202 was not a well-controlled study. Most cited problems with the controls. One member explained that a historically-controlled study *could* provide evidence of effectiveness, but that Study 202 did not. Two committee members noted that the original placebo-controlled portion of the study was

Figure 15: Study 201/202 – Individual NSAA Performance by Age



negative. One member who cited issues with the controls also noted that a single trial would be insufficient to provide substantial evidence.

The 3 members who voted that there was substantial evidence of effectiveness explained that the study results correlated with the testimonies presented by the public.

Commentary:

I agree with the Division, the Office of Biometrics, the Office of Clinical Pharmacology, and the Advisory Committee with respect to the lack of substantial evidence of effectiveness for eteplirsen. The review team elaborates on many factors that differ, or could differ, between the treatment groups – factors that could lead to a difference in outcomes. Externally-controlled trials are best-suited for diseases where progression is highly predictable and treatment effects are extreme. Although there appeared to be a difference in ambulation between patients in Study 202 and patients in the external control group, the effect size was not sufficient to be persuasive, given the inability to control bias in an externally-controlled study. As explained in ICH E10, "...the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." With only 12 patients in the trial and a moderate difference in walking velocity, the study falls short.

Finally, it is critical to note that no dose-limiting side effects were observed at either dose tested in Study 201/202, and even the most optimistic interpretation of the data is that patients experienced gradual decline in function – not stabilization. Even if one were to reach the conclusion that the applicant showed substantial evidence of dystrophin production, deserving of accelerated approval, investigation of higher doses would be imperative.

8. Safety

As explained in the clinical review, the number of subjects exposed was too small to provide an adequate assessment of safety. On the other hand, I also agree with the review team that the deficiencies in safety assessments would not likely be an issue for approvability in their own right had the drug been demonstrated to be effective. In other words, for a therapy that is shown to be effective in a serious condition where there are no approved drugs, we would approve a marketing application even with substantial risks, as long as we could write adequate instructions for use. Moreover, we would not delay approval of a marketing application because of uncertainty of risks. Instead, we would work with the applicant to obtain more extensive safety data post-approval. Such would be the case for this application if there were substantial evidence of effectiveness.

Of note, many patients in these studies are now receiving infusions through chronic indwelling catheters. Although we are not aware of any serious adverse events caused by infections, with approval of this drug there would undoubtedly be serious infections and possibly rare deaths eventually. The risk of an indwelling IV line in patients on chronic corticosteroids should be mentioned in labeling if the drug is approved.

Although neither immunogenicity nor allergic reactions have been reported with eteplirsen, immunogenicity testing would be advisable in ongoing trials. Moreover, given that these

patients may be naïve to Becker-type dystrophin, the potential for anti-dystrophin antibodies should be studied as well.

9. Advisory Committee Meeting

There were many important discussions at the April 25, 2016 Advisory Committee Meeting, and they are summarized above, in context.

10. Pediatrics

Duchenne Muscular Dystrophy is an orphan indication, not subject to the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

Site Inspections:

The site at Nationwide Children’s Hospital was inspected in 2014. See description and conclusions in Section 7, above, and, in particular, the summation and discussion in Dr. Breder’s review.

Dr. Ashutosh Rao conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) of the facilities at University of Iowa in Iowa City, IA and Sarepta Therapeutics Inc. in Corvallis, OR. The inspections confirmed that the blinding procedure, handling of the sample shipment, and the conduct of Western blot analyses of the samples from Study 301 (PROMOVI) were consistent as predefined in the protocol.

Name Review:

The Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, “EXONDYS 51,” is acceptable from both a promotional and safety perspective.

12. Labeling

I do not recommend approval, but if the drug were to be approved, the label would need to state that no clinical benefit has been established, and explain the effect on the surrogate endpoint in clearly understandable language (i.e., 0.3% or 3 parts in a thousand). Section 6 would need to note that safety is not well characterized.

13. Decision/Action

DMD is a rare genetic disease characterized by the near absence of functional dystrophin protein, leading inexorably to myocyte degeneration, muscle dysfunction and inflammation, severe disability, and death, robbing patients of their dignity along the way. Although steroids are thought to slow the course of the disease and are typically considered standard of care, they are by no means curative, and they have their own side effects.

The cause of DMD is well established – the absence of structural dystrophin protein in myocytes. There is wide belief in the medical/scientific community that restoration of functional dystrophin protein has a strong potential to ameliorate the disease.

Eteplirsen is a novel PMO that is designed to lead to translation of an abnormal but functional dystrophin protein – a protein that is produced in Becker muscular dystrophy, a far less severe form of muscular dystrophy. The data from RT-PCR show that the drug produces the intended Becker-type messenger RNA; we have no data on the extent of messenger RNA production.

As noted by the review team, the clinical data generated from study 201/202 do not provide evidence of efficacy. The aim of Study 201, the only randomized placebo-controlled study conducted by the applicant, was to assess dystrophin production in response to lower and higher eteplirsen regimens (30 or 50 mg/kg/week) vs. placebo. Results of the original analyses of Study 201, published in a major journal, were remarkably positive, and their publication led to widespread enthusiasm for the drug. Unfortunately, an FDA inspection found a number of important technical factors that rendered the data unreliable and uninterpretable: the Western blot analyses were sub-standard; there were also critical problems with the reading of the immunohistochemistry images. FDA recommended a blinded re-read of the images, but upon re-read of the images by 3 blinded pathologists using FDA-recommended procedures, there was no increase in dystrophin production.

Likewise, Study 201 did not meet its 1^o clinical endpoint, 6MWT, at Week 24. Two patients in the low-dose eteplirsen group became unable to ambulate early in the study, such that a proper intent-to-treat analysis of the 6-minute walk data nearly showed a statistically significant difference in favor of *placebo*.

The applicant switched all patients to active drug in Study 202, and has continued to follow the patients for 6-minute walk distance, NSAA, and rise time.

Study 202 did not meet its 1^o clinical endpoint, 6MWT, at 48 weeks.

The alternative analyses of Study 202 proposed by the applicant are based on comparison to an external control group obtained from registry patients in Italy and Belgium. Questions about comparability notwithstanding, analyses have not shown a clear separation of the disease course between eteplirsen-treated patients and external controls. Moreover, there is not a clear separation between eteplirsen-treated patients and patients in the CINRG registry. Thus, neither external control group suggests there is a treatment effect.

The Western blot analyses from Week 180 of Study 201/202 showed a low quantity (0.9%) of dystrophin; however, the study was not adequate and well controlled (the baseline level of dystrophin was not known with certainty), and the lack of correlation between results of Western blot and immunohistochemistry demonstrates a troubling lack of internal consistency.

Study 301, on the other hand, was an adequate and well-controlled study that provided substantial evidence of Becker-type dystrophin production in response to eteplirsen. The mean change in Becker-type dystrophin with treatment was 0.22% to 0.32%, depending on the method used to impute values less than the lower limit of quantification. Although all members of the review team believe that Becker-type dystrophin is an appropriate surrogate endpoint, the mean quantity of dystrophin produced in Study 301 was minute by any standard. In considering

responders, even the largest responder in Study 301 produced only 1.33% of normal dystrophin, which is thought by many authorities to be insufficient. No other patient produced 1% dystrophin in response to treatment.

Recognizing that the threshold for the effect size needed to be 'reasonably likely' to predict clinical benefit is not known, the view provided in the literature suggests that at least 3% of normal dystrophin is inadequate, and levels perhaps much more, a minimum of 10%, would be necessary for detectable clinical benefit. The finding in Study 301, an increase in the range of 0.22 to 0.32% of normal, is an order of magnitude below this level.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will be capable of ameliorating the fundamental genetic defect of DMD, but the effect size seems insufficient at the tested doses.

Various individuals have opined that there appears to be some evidence that some patients are producing dystrophin in response to eteplirsen; however, such optimism fails to reach the legal threshold of 'reasonably likely to predict clinical benefit' required for accelerated approval.

Accelerated approval of this NDA based primarily on the change in Becker-type dystrophin in Study 301 would be problematic for these reasons:

1. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.22% is considered adequate to support accelerated approval, then the question arises as to whether there is any statistically significant change that would be too small to support accelerated approval. Similarly, if a response had been defined as a treatment effect of 1%, there would have been only one (out of 12) responders in Study 301.

If we were to adopt the concept that, for rare diseases, accelerated approval can be supported by any statistically significant change in an appropriate surrogate (or by a response in a single patient), we would enable accelerated approval of numerous drugs for rare diseases. No doubt there are some who would applaud this as a regulatory advance, but these are typically the kinds of findings that support Breakthrough Designation, not approval. If accelerated approval based on any change in a surrogate endpoint is what is meant by regulatory flexibility and this is the new normal, a new approval pathway is clearly needed.

With lowering of the standard for accelerated approval, the result would be a world where traditional clinical trials are abandoned in favor of small proof-of-concept studies designed to show any level of production of a target protein – e.g., a statistically significant effect in a paired pre- vs. post-treatment analysis that is clinically meaningless. There would be no reason to pursue placebo-controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a substantial disincentive to the conduct of such trials. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.

2. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, the dose is sub-therapeutic. Moreover, the short 3.5-hour half-life of eteplirsen by no means supports a weekly dosing regimen. I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic.

Imagine that 100 years ago a promising drug called penicillin is discovered – a potential cure for pneumococcal pneumonia – but the drug is difficult to produce and expensive. A dose of 5 mg weekly has been shown to have statistically significant bactericidal effects on *Streptococcus pneumoniae*. Would it be ethical to give the drug accelerated approval based on this finding and allow marketing of a dose of 5 mg, absent additional information? (The therapeutic dose is ~2 logs higher than 5 mg.) Patients who might receive a lifesaving therapy (i.e., a higher dose) would die because the dose is too low.

Despite considerable pressure from the DMD patient community and many well-intentioned members of the public who have lobbied on their behalf, I am unable to reach the conclusion that the applicant has provided substantial evidence to support either conventional or accelerated approval of eteplirsen for the treatment of DMD. This view is in agreement with the unanimous opinions of members of the review team from the Division of Neurology Products, the clinical pharmacology review team, and the biostatistics review team. The Advisory Committee was under intense and near-incessant pressure from a large public audience, urging them to believe that eteplirsen was effective, and life changing in some circumstances. Emotions in the room ran high. In spite of this pressure, that majority of the Advisory Committee voted against both conventional and accelerated approval.

In a June 3, 2016 letter from Dr. Janet Woodcock, the applicant was advised that “If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval....” It is difficult to consider production of 2 to 3 parts per thousand as a “meaningful” change. To put this effect into perspective, if a normal amount of dystrophin were equivalent to a \$5 bill, this change would be equivalent to a penny.

With all of this information at hand, most sponsors would have concluded that exploration of higher doses was needed; however, this applicant chose instead to trumpet the preliminary findings from their 12-patient phase 1/2 study, convincing many in the DMD community that the drug was highly effective, and unleashing a public media campaign (with support of many politicians) to approve the drug. The reality is that FDA is a science-based organization. We do not – and should not – make approval decisions based on patient anecdotes or campaigns through social media.

I strongly agree with the decisions of Dr. Bastings, reviewer staff in the Division, the Office of Biometrics, and the Office of Clinical Pharmacology to issue a complete response for this NDA. I also agree that it would be desirable to provide access to this drug for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

Path Forward:

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at a dose of 30 and 50 mg/kg/week are adequate, but they do not support efficacy.

We remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the 1° endpoint, again, testing higher doses.

The applicant is continuing to enroll the PROMOVI study, an open-label, multi-center, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

The 1° endpoint is change in 6-minute walk test distance from baseline. A 2° endpoint is the percentage of dystrophin-positive fibers, as assessed by immunohistochemistry. Patients undergo muscle biopsies at baseline and various time points to assess dystrophin production.

My suggestion for a path to approval is to randomize patients in the ongoing PROMOVI study to:

- 1) remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blind to treatment group. For accelerated approval, the 1° endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the 1° endpoint would be a test(s) of physical performance such as rise time or the NSAA.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, want to know if higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients assigned to placebo, this concern would not exist in this study. And if the applicant were to forego immunohistochemistry studies, needle biopsies with local anesthesia (rather than open biopsies under more intensive anesthesia) would be sufficient.

This study design would simultaneously address another concern that I believe has been underappreciated by many. As noted above, it would be problematic in my view to approve a dose of 30 mg/kg/week, presumably leading to a dystrophin increase of ~0.3%, when it is

known that this dose fails to prevent the decline in physical function and yet produces no overt toxicity. The monkey data (Table 1) suggest that much higher doses might have a far greater effect on exon skipping, an impact that might prevent disease progression. Thus, it seems imperative to study higher exposures.

14. Final

Many of us would wish to approve this drug if we could. DMD is a horrible disease and there are no approved treatments. FDA takes seriously the patient perspective and our congressional mandate to be flexible. But patient-focused drug development is about listening to patient perspectives about what matters to them; it is not about basing drug approvals on anecdotal testimony that is not corroborated by data.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

From: [Unger, Ellis](#)
To: [Woodcock, Janet](#); [Jenkins, John K](#); [Temple, Robert](#); [Dunn, Billy](#); [Bastings, Eric](#)
Subject: Re: Final Memo on Sarepta
Date: Friday, July 15, 2016 9:34:16 AM

I'll be appealing. I'm writing it now. I'll do the best I can in terms of time, but I can't rush through it.

Sent from my BlackBerry.

From: Woodcock, Janet
Sent: Friday, July 15, 2016 7:56 AM
To: Jenkins, John K; Unger, Ellis; Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: Final Memo on Sarepta

I entered my final memo into DAARTs yesterday. Anyone who plans to appeal can do so now. I would appreciate that this be done promptly if it is planned. Janet Woodcock

11 pages of draft labeling have been withheld as b(5) immediately following this page

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: RE: Sareptafinal (6).docx
Date: Thursday, July 14, 2016 2:42:04 PM

Document uploaded and signed into DARRTS! I believe you received an email communication.

P.S. if you access the intranet, you no longer should see the box that requires you to enter your PIV badge credentials.

Sharnell

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 12:00 PM
To: Ligon, Sharnell (CDER)
Subject: RE: Sareptafinal (6).docx

Thanks you! jw

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 11:59 AM
To: Woodcock, Janet
Subject: Sareptafinal (6).docx

Attached is the final clean document.

From: [Unger, Ellis](#)
To: [Woodcock, Janet](#)
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw
Date: Thursday, July 14, 2016 1:28:12 PM

OK – I see the NSAA data – they are in appendix 5 of the briefing document. Thanks!

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 12:58 PM
To: Unger, Ellis
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw

No, for the Advisory committee meeting. jw

From: Unger, Ellis
Sent: Thursday, July 14, 2016 12:06 PM
To: Woodcock, Janet
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw

Was this a briefing document they provided for us for a meeting?

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 12:02 PM
To: Unger, Ellis
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw

I put my own analysis back in and cited the sources of the data, from the firm's briefing document. Sorry I misunderstood what you were saying. jw

From: Unger, Ellis
Sent: Thursday, July 14, 2016 11:09 AM
To: Woodcock, Janet
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw

Thanks, Janet.

You can put in any data you think are best, but I think you will want to cite the source of the data. Or, if it was your own analysis, explain what you did so others can follow it.

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 11:06 AM
To: Unger, Ellis
Subject: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: Sareptafinal (6).docx
Date: Thursday, July 14, 2016 11:59:28 AM
Attachments: [Sareptafinal \(6\).docx](#)

Attached is the final clean document.

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER),
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 in 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 ICH 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% 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 factors.

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 CK, 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 eteplirsen with Francesco Muntoni's group 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 α -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. 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 corrected 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, data from Dr. Unger) 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.

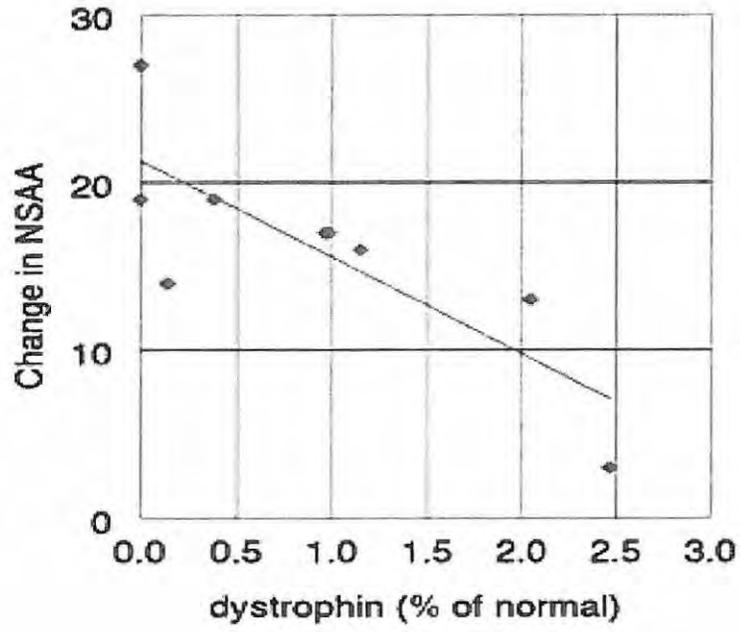
COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

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.

Figure 1



From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: RE: Sarepta Document / Dr. Woodcock's memo
Date: Thursday, July 14, 2016 11:07:24 AM
Attachments: [Sareptafinal.docx](#)

Sure. Please see attached.

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 11:07 AM
To: Ligon, Sharnell (CDER)
Subject: RE: Sarepta Document / Dr. Woodcock's memo

Can you send me the document? TX jw

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 11:00 AM
To: Woodcock, Janet
Subject: FW: Sarepta Document / Dr. Woodcock's memo

Hi Dr. Woodcock,

Please see comments below from Dr. Unger. Do you need my assistance?

Thanks

Sharnell

From: Unger, Ellis
Sent: Thursday, July 14, 2016 10:58 AM
To: Ligon, Sharnell (CDER)
Cc: Choy, Fannie (Yuet); Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert; Jenkins, John K
Subject: RE: Sarepta Document / Dr. Woodcock's memo

Sharnell,

Here are my comments:

Page 6, line 2, change "ICH" to "IHC"

Page 8, under f, "27patients" → "27 patients"

Page 9, under l, fix " -sarcoglycan"

Page 10, There is an incorrect statement here. The memo states: "There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1, data from Dr. Unger) "

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Ellis

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Evaluation and Research
US FDA

From: Choy, Fannie (Yuet)
Sent: Thursday, July 14, 2016 9:30 AM
To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Importance: High

Morning,

Please see attached email.

Thanks
Fannie

From: Ligon, Sharnell (CDER)
Sent: Thursday, July 14, 2016 9:09 AM
To: Choy, Fannie (Yuet)
Subject: Sarepta Document
Importance: High

Dear Fannie,

Attached, please find Dr. Woodcock's final Sarepta document. Do you mind checking with the Dr. Unger and the division to see if they have any comments before it is entered into DARRTS? Additionally, will you be the one uploading this document into DARRTS so Dr. Woodcock can sign off on it?

Thanks

Sharnell



NDA 206488

GENERAL ADVICE

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

This letter is in response to your email of June 2, 2016, to Janet Woodcock, M.D., in which you agreed to perform Western blots on baseline and Week 48 biopsies from eteplirsen-treated patients to assess dystrophin content. We will work with you on the protocol and analysis plan, and on the dates for FDA observers to be present during the procedures.

We agree to have an FDA observer present at the Iowa site to monitor tissue sampling and blinding procedures, and to have an observer present at the Corvallis site during performance of the Western blot procedure. We also understand that Corvallis is not a GLP facility.

We understand that a new normal control will need to be established to generate the standard curve of a serially-diluted normal comparator as part of these procedures. Please confirm the healthy dystrophin genotype and phenotype of this new control and compare side-by-side with the limited previous healthy control you have available. Confirm that the validation parameters and acceptance criteria for the new healthy control are comparable to those for the previous healthy control used with the Week 180 samples (e.g., linearity of the serially diluted sample, %RSD).

You should provide each of the relevant protocols for our review that describe the methods you propose to use for testing dystrophin, including those related to tissue acquisition at the clinical site(s), processing, blinding, and shipping procedures at the University of Iowa or elsewhere, tissue quality control before analysis, validation of the new normal control, and Western blotting at the Corvallis location.

You should implement appropriate quality control measures including strict blinding procedures to ensure that the integrity of the other primary and secondary assessments is not compromised as a result of this specific dystrophin investigation.

If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to

grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).

To allow for prompt approval, should your dystrophin analysis prove successful, we will work with you over the next several weeks on completing labeling negotiations to the degree possible and on necessary postmarketing requirements and commitments.

We request that you not publicly communicate the specific details of this plan until after completion in order to allow maximum procedural efficiency.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
06/03/2016

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Date: Thursday, July 14, 2016 11:00:19 AM

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Sharnell

From: Unger, Ellis
Sent: Thursday, July 14, 2016 10:58 AM
To: Ligon, Sharnell (CDER)
Cc: Choy, Fannie (Yuet); Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert; Jenkins, John K
Subject: RE: Sarepta Document / Dr. Woodcock's memo

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Director
Office of Drug Evaluation-I
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Sent: Thursday, July 14, 2016 9:30 AM

To: Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Temple, Robert
Cc: Choy, Fannie (Yuet)
Subject: FW: Sarepta Document / Dr. Woodcock's memo
Importance: High

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Thanks
Fannie

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Sent: Thursday, July 14, 2016 9:09 AM
To: Choy, Fannie (Yuet)
Subject: Sarepta Document
Importance: High

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Thanks

Sharnell

From: [Unger, Ellis](#)
To: [Woodcock, Janet](#)
Subject: RE: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out. jw
Date: Thursday, July 14, 2016 11:09:01 AM

Thanks, Janet.

You can put in any data you think are best, but I think you will want to cite the source of the data. Or, if it was your own analysis, explain what you did so others can follow it.

From: Woodcock, Janet
Sent: Thursday, July 14, 2016 11:06 AM
To: Unger, Ellis
Subject: sorry Ellis, I thought you said you got that data from the week 240 cohort. I'll just take it out.
jw

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: Sareptafinal.docx
Date: Thursday, July 14, 2016 8:32:43 AM
Attachments: [Sareptafinal.docx](#)

Please see attached.

CENTER DIRECTOR DECISIONAL MEMO

NDA# **206488**

Drug Name **EXONDYS 51 (eteplirsen)**

Indication **Duchenne Muscular Dystrophy (DMD)**

Sponsor **Sarepta**

Author **Janet Woodcock, M.D.**
Director, Center for Drug Evaluation and Research (CDER),
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 α -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. 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 corrected 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, data from Dr. Unger) 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.

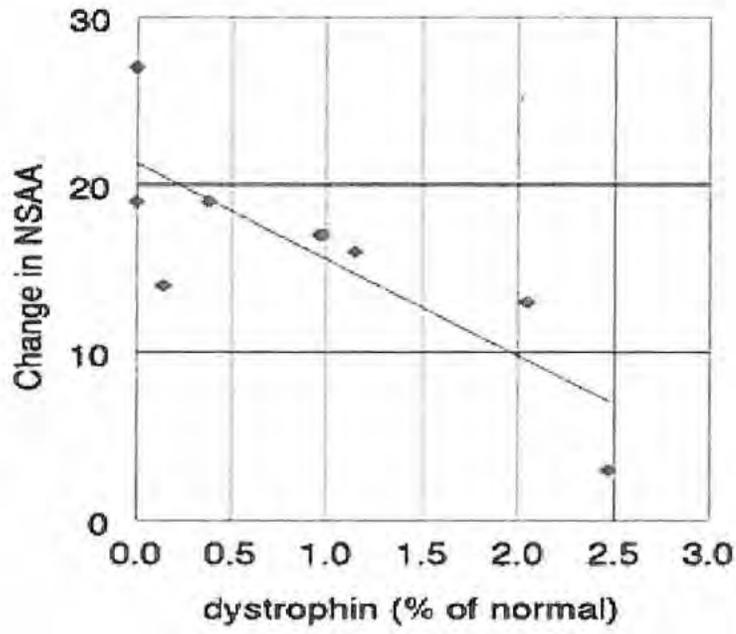
COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

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.

Figure 1



Appears this way on the original

From: [Buckman-Garner, ShaAvhrée](#)
To: [Woodcock, Janet](#)
Subject: Sarepta
Date: Wednesday, July 13, 2016 7:12:05 PM
Attachments: [Sarepta_dct.docx](#)

Hi Janet,

Thanks for allowing me to take a look at this. I think you support your key points clearly. I did track some minor suggested edits for readability and identified a couple of critical points that you may want to reword to make sure they are clear to the reader. This is a very challenging space and I support your difficult decision given the assay limitations, limited sample sizes, and the lack available therapies for a disease with no other options, as well as the opportunities for further exploration.

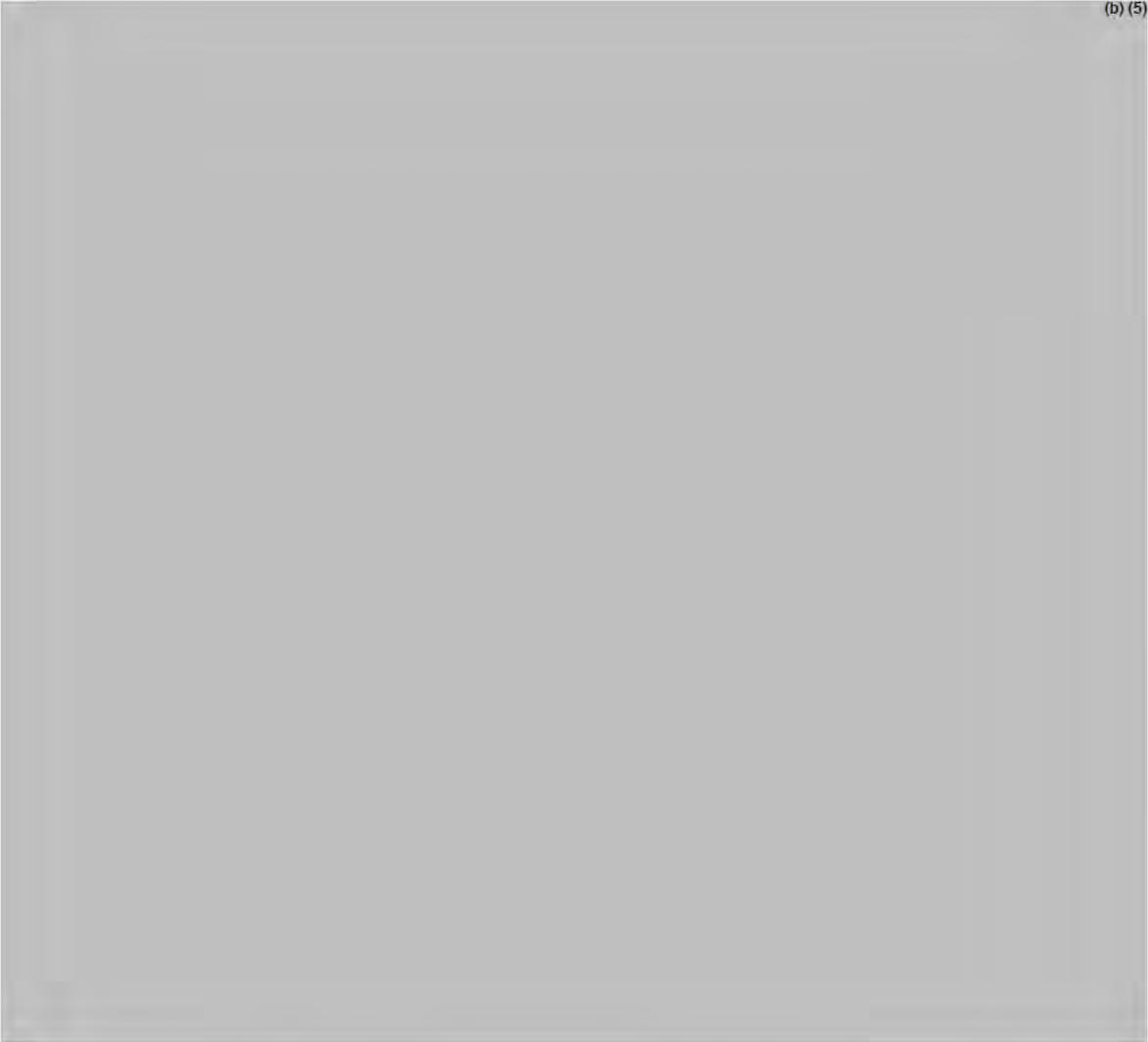
Hope my comments are helpful.

ShaAvhree

Center Director Decisional Memo DRAFT

NDA# 206488
Drug Name: EXONDYS 51™ (eteplirsen)
Indication: Duchenne Muscular Dystrophy (DMD)
Sponsor: Sarepta
Author: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research,
FDA

(b) (5)



16 pages of draft language have been withheld as b(5) immediately following this page

From: [Ligon, Sharnell \(CDER\)](#)
To: [Woodcock, Janet](#)
Subject: Sarepta dct.docx
Date: Wednesday, July 13, 2016 5:23:55 PM
Attachments: [Sarepta dct.docx](#)

Please see attached. Is this okay or would you like me to expand the graph?

Thanks

Sharnell

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director, DNP
Subject	Division Director Summary Review
NDA/BLA #	206488
applicant	Sarepta Therapeutics, Inc.
Date of Submission	June 26, 2016
PDUFA Goal Date	May 26, 2016
Proprietary Name / Non-Proprietary Name	Exondys 51 Eteplirsen
Dosage Form(s) / Strength(s)	Solution/ 30 mg/kg intravenously once-weekly
applicant Proposed Indication(s)/Population(s)	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
Recommended Action:	Complete Response
Approved/Recommended Indication/Population(s)	None

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Project Manager	Yuet (Fannie) Choy; Laurie Kelley
Medical Officer Clinical Review	Christopher Breder
Clinical Pharmacology Review	Ta-Chen Wu; Yuxin (Angela) Men, Venkatesh (Atul) Bhattaram; Kevin Krudys; Hobart Rogers; Christian Grimstein; Mehul Mehta
Statistical Review	Xiang Ling; Kun Jin; Hsien Ming (Jim) Hung
Pharmacology Toxicology	David Hawver; Lois Freed; Paul Brown
Office of Biotechnology Products (Bioassay)	Ashutosh Rao; Amy Rosenberg
OPQ/Chemistry Manufacturing and Controls	Joseph Leginus; Donna Christner; Mariappan Chelliah; Denise Miller; Neal Sweeney; Sung Kim; Edwin Jao; Zhong Li; Zhihao Peter Qiu; Dahlia Woody; Martha Heimann; Wendy Wilson-Lee
OPQ / Environmental Assessment	James Laurenson; M. Scott Furness
Method Validation	Michael Hadwiger; Michael Trehy
Statistical Review – Stability data	Zhuang Miao; Xiaoyu Dong, Meiyu Shen; Yi Tsong
Controlled Substance Staff	Katherine Bonson; Martin Rusinowitz; Michael Klein; Sandy Saltz
Office of Scientific Investigation	Antoine El Hage; Cara Alfaro; Susan Thompson; Kassa Ayalew; Ni Aye Khin
Division of Advisory Committee and Consultant Management	Diem Ngo; Moon Hee Choi

Office of Prescription Drug Promotion	Aline Moukhtara
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Division of Risk Management	Robert Pratt; Jamie Wilkins Parker; Kellie Taylor; Cynthia LaCivita
Associate Director for Labeling, DNP	Tracy Peters
Cross-Discipline Team Leader	Ronald Farkas

1. Benefit-Risk Assessment



Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • Duchenne Muscular Dystrophy (DMS) is a degenerative X-linked recessive genetic disorder associated with mutations in the dystrophin that result in the absence or near absence of functional dystrophin protein. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. • Exon 51 skip-amenable DMD, a subgroup of DMD, is defined by the presence of exon 51 in the dystrophin gene and the deletion of one or more exons contiguous with exon 51, resulting in an out-of-frame deletion in which the reading frame is potentially restorable by the skipping (removing) of exon-51. Mutations that are potentially treatable by skipping exon 51 are thought to comprise about 13% of the DMD population, resulting in a prevalence of about 2000 boys in the US. • Loss of muscle strength is progressive, typically beginning a waddling gait and inability to jump in young boys, progressing to a loss of ability to ambulate. The loss of ambulation is generally considered to occur between ages 8 to 16 years, but about 25% of patients may still be ambulatory at age 16. While pulmonary and cardiac function are generally normal during early childhood, 	<p>DMD is a serious and life-threatening disease. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens, followed by decline in respiratory and cardiac function, resulting in death typically in the third decade.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.</p>	
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> There is no FDA-approved treatment for DMD. The current standard of care is glucocorticoids, which are thought to provide a modest beneficial effect on function and survival. In addition, supportive care, such as assisted ventilation and physiotherapy, is modestly effective in prolonging function and survival. 	<p>There is a substantial unmet need for therapies in DMD.</p>
<p>Benefit</p>	<ul style="list-style-type: none"> Clinical efficacy was evaluated in a 24 week placebo-controlled trial (Study 201), which was followed by open-label extension (Study 202, for which data up to Week 240 have been submitted to the application). Study 201 was negative. The applicant has requested accelerated approval based on an endpoint of 6-minute walk distance in Study 202, comparing open-label experience with two dose levels of eteplirsen (30 mg/kg and 50 mg/kg weekly) to an external historical control. The applicant proposes that 6-minute walk be considered an intermediate endpoint demonstrating delayed disease progression. The division considers an effect on walking distance to be a clinical benefit that, if demonstrated, would support full approval. Therefore, the division sees no justification for using 6-minute walk distance as an intermediate endpoint here, in particular as the period of observation is unusually long, around 4 years, which is more than sufficient to identify a possible clinical benefit. The clinical evidence provided by the applicant, which includes a number of clinically meaningful endpoints, is therefore to be examined in the context of “conventional” approval. The comparison to historical control made by the applicant in Study 202 failed to show a 	<p>The applicant has not provided substantial evidence of efficacy from adequate and well controlled trials to support “conventional” approval.</p> <p>The applicant has provided substantial evidence that eteplirsen induces production of dystrophin. This is unprecedented for Duchenne Muscular Dystrophy, establishes proof of concept, and gives hope that this therapeutic approach may address the fundamental pathology of DMD. However, the amount of dystrophin produced in response to eteplirsen treatment is very small. While it is somewhat possible that the amount of dystrophin produced may lead to a modest clinical benefit, such a benefit does not appear reasonably likely.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>clear separation between the disease course in eteplirsen-treated patients and historical control patients. Instead, all patients in the eteplirsen treatment group appeared to experience the sequential worsening of functional abilities and muscle weakness expected in patients with Duchenne muscular dystrophy.</p> <ul style="list-style-type: none"> • Biomarkers that reliably reflect the health and amount of skeletal muscle may, if supported by sufficient scientific evidence and acceptable analytical methods, be used as surrogate endpoints to support accelerated approval of a new drug for Duchenne muscular dystrophy. Such a biomarker would have to be “reasonably likely to predict clinical benefit” in order to be acceptable as a basis for accelerated approval. In Study 201/202, the applicant obtained 4 muscle biopsies, spaced between baseline (pre-treatment) and Week 180 of treatment. Pharmacodynamic effects of eteplirsen are potentially demonstrable at two levels: expression of an altered messenger RNA in muscle, and production of dystrophin protein in muscle. There is evidence of production of an altered messenger RNA in the muscle of all patients of Study 201/202. However, this biomarker provides little support of efficacy for eteplirsen. Demonstration of messenger RNA production is necessary to establishing proof of concept, but not sufficient. In Study 201/202, the mean dystrophin level in patients who have been treated with eteplirsen for three and a half years was 0.93% ± 0.84% of normal. As baseline dystrophin level was only available in two of these patients, and because of methodological issues, it was difficult to ascertain whether there was any increase from baseline in dystrophin in Study 201/202. Therefore, the applicant was asked to provide additional dystrophin data from an additional 13 patients participating in an ongoing study (PROMOVI study) and who had a muscle biopsy at baseline and at Week 48 (with data available in 12 of those patients). In those 12 patients, there was a small (mean = 0.3%) 	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>but statistically significant increase from baseline in dystrophin level. Overall, the applicant has provided substantial evidence that eteplirsen produces an increase in dystrophin, but the mean increase is very small. Based on a comparison of Week 48 to baseline using reported dystrophin values, most patients (about 60%) from the PROMOVI study had no increase in dystrophin content, or an increase smaller than 0.25% of normal levels. A single patient in the PROMOVI study had a dystrophin increase greater than 1%, and no patient had a dystrophin increase greater than 2%. In comparison, about a third of patients from Study 201/202 had no increase in dystrophin content, or an increase smaller than 0.25% of normal levels, while about a third of patients had dystrophin increases greater than 1% of normal levels. A single patient had a dystrophin increase greater than 2%, and no patient had a dystrophin increase greater than 3%. The minimum level of dystrophin that might be reasonably likely to predict clinical benefit in patients with DMD remains unknown, and there are no data to support the concept that the small increase in dystrophin induced by eteplirsen at the doses that were studied is reasonably likely to predict clinical benefit. In Study 201/202, there was no correlation between dystrophin levels and clinical outcome, and no dose-response in the amount of dystrophin.</p>	
Risk	<ul style="list-style-type: none"> The clinical safety database for eteplirsen is small: 114 total patients exposed, with only 36 exposed for ≥ 24 weeks and 12 exposed for ≥ 1 year. Most of these exposures were outside of placebo-controlled studies, limiting ability to determine if adverse events were the result of drug effect or chance. However, the serious and severe adverse events that occurred were generally consistent with events expected in DMD. The 12 patients in Study 202 were exposed for >3 years, which provides some reassurance against delayed toxicity. 	<p>The safety database for patients exposed at the intended dose is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> In animal studies, the primary target organ was the kidney, with dose-dependent renal tubular cytoplasmic basophilia and/or vacuolation and, at the high dose, tubular degeneration/necrosis. In a mouse study, dilatation of the lateral ventricles of the brain was observed at the mid and high doses. The mechanism of this effect, and its relevance to humans, is unknown. Mean eteplirsen plasma exposures (AUC) at the NOAELs for monkey and juvenile rat were 20-fold and 6-fold, respectively, greater than that in patients dosed once weekly with 30 mg/kg IV eteplirsen. 	
Risk Management	<ul style="list-style-type: none"> Safety risks have not been identified that would require risk management beyond standard pharmacovigilance. A patient registry may be useful to acquired additional safety information in the postmarketing setting. 	Safety risks have not been identified that would require risk management beyond standard pharmacovigilance.

2. Background

The NDA under review is for eteplirsen, proposed for the treatment of patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping ($\approx 13\%$ of patients with DMD).

Duchenne Muscular Dystrophy (DMS) is a fatal, degenerative, X-linked recessive genetic disorder associated with mutations in the gene encoding dystrophin, a sarcolemma protein critical to the structural stability of myofibers in skeletal and cardiac muscle. Dystrophin mutations induce a shift in the open reading frame of the dystrophin transcript, leading to a reduction or absence of functional dystrophin. In the absence of dystrophin, the stress of muscle contraction causes progressive muscle damage. Duchenne muscular dystrophy is usually first diagnosed before age 5. Progression in DMD occurs in a generally predictable stepwise fashion, starting with loss of ability to stand from the floor, followed by a loss of ability to walk independently, itself preceding a decline in pulmonary function.

There are no drugs approved for the treatment of DMD, and there is an enormous unmet medical need. Corticosteroids are standard of care for the condition, and appear to slow down progression, but they have many side effects.

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature spliced mRNA, thereby restoring the mRNA reading frame. If successful, this shift may enable the production of a truncated dystrophin protein, which, if functional, may lead to clinical benefit.

Pharmacodynamic and clinical effects of eteplirsen are therefore potentially demonstrable at three levels: expression of an altered messenger RNA for dystrophin in muscle (assessed by nested polymerase chain reaction [PCR]), production of dystrophin protein in muscle, and improvement or preservation of muscle function.

The applicant undertook two exploratory studies (Study 28 and Study 33) to assess eteplirsen's potential to increase expression of an altered mRNA and dystrophin expression, and a 12-patient controlled clinical study (Study 201/202) to assess whether eteplirsen increased expression of dystrophin protein, and led to clinical benefit.

Study 201/202 began as a 24-week randomized placebo-controlled study (Study 201). After Study 201 did not meet its primary endpoint, and as FDA did not consider the post hoc analyses of Study 201/202 conducted by the applicant to be scientifically valid, FDA advised the applicant to conduct an adequately powered, randomized, placebo-controlled trial to assess the clinical benefit of eteplirsen. But in the context of an ongoing series of reports from the applicant and its academic associates describing marked effects on dystrophin production and

stabilization of disease progression, many in the DMD community had strong reservations regarding the ethics and practicality of conducting another placebo-controlled trial of eteplirsen. Given the apparent difficulty of doing such a trial, FDA expressed willingness to consider an externally controlled trial, although stating clearly that interpretation of the data could be difficult, and that the acceptability of the study would be a matter for NDA review. FDA advised the applicant to identify external control groups appropriately matched to Study 202 patients, including similar treatment modalities, and to provide patient-level data. The applicant identified two DMD patient registries as a source of external data, the “Italian DMD Registry” and the “Leuven Neuromuscular Reference Center” registry, and conducted a post hoc comparison of the patients in Study 201/202 with patients from the two external registries.

The applicant is proposing approval primarily based on a post hoc comparison of patients of all available open-label data from Study 202 (up to Week 144) to a natural history cohort of untreated patients. The applicant believes that the results of their external control comparison provide evidence of benefit on an “intermediate clinical endpoint” – a clinical endpoint that can be measured earlier than irreversible morbidity or mortality – that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and that could suffice as a basis for accelerated approval.

3. Product Quality

From a product quality perspective, NDA 206488 is recommended for approval.

Drug substance

As discussed by the product quality reviewer, eteplirsen contains a sequence of 30 linked (b) (4) phosphorodiamidate morpholino subunits. (b) (4)

The chemical name for eteplirsen is:

(b) (4)

Drug Product

Eteplirsen injection is a sterile solution containing 50 mg eteplirsen per mL. The applicant proposes two single dose vial configurations: 100 mg/2 mL and 500 mg/10 mL. All excipients are within the ranges used in previously approved intravenous drug products.

The product must be diluted with saline prior to infusion. The product does not contain an antimicrobial preservative and should be used within 4 hours after dilution if stored at room temperature, or 24 hours after dilution if refrigerated.

Based on evaluation of stability data from primary and supportive batches, an expiration dating period of 18 months is established for eteplirsen, when stored refrigerated (5°C).

The inspection of the drug substance and of the drug product manufacturing facilities is acceptable.

The applicant has agreed to the following CMC post-marketing commitments:

1. Investigate the root cause of the increasing assay trend observed in the drug product stability study.
2. Revalidate the accuracy of the in-process (b) (4) method used during drug product manufacture.
3. Revalidate the robustness of the in-process (b) (4) method in terms of (b) (4) (b) (4).
4. Investigate the consistent bias in the in-process (b) (4) results and the release (b) (4) (b) (4) results.

5. Nonclinical Pharmacology/Toxicology

From a nonclinical perspective, NDA 206488 is recommended for approval.

Dr. Hawver, nonclinical reviewer, notes that pharmacological studies have demonstrated that administration of eteplirsen can induce exon 51 skipping in dystrophin mRNA in human muscle cell cultures, muscle explant cultures, in transgenic hDMD mice, and in cynomolgus monkeys.

In cynomolgus monkeys, samples of quadriceps muscle, heart, and diaphragm tissues, collected from cynomolgus monkeys after 12 weekly doses of eteplirsen at 0, 5, 40, or 320 mg/kg IV, or 320 mg/kg SC. The samples were analyzed using PCR for exon 51 skipping of the dystrophin gene. Dr. Hawver discusses that all three target muscles showed increased skipping of exon 51 of the dystrophin gene after treatment with IV or SC eteplirsen. There is also a very clear dose-response in exon 51 skipping, as shown in Table 1, which is adapted from Dr. Hawver's review. Of note, a similar dose response was observed in DMD patients in exploratory Study 33 (see Clinical/Statistical-Efficacy), in which direct intramuscular injection of eteplirsen led to increased skipping of exon 51 in all five patients at a 0.9 mg dose, but not in patients injected with 0.09 mg eteplirsen or placebo. Similarly, dystrophin expression by western blot was noted in all patients treated with 0.9 mg of eteplirsen, but in no patient who received with 0.09 mg of eteplirsen. On immunofluorescence testing, there was also a high

percentage of dystrophin-positive fibers with eteplirsen 0.9 mg (ranging from 44 to 79%), versus no expression with eteplirsen 0.09 mg.

Table 1: Dose-response on exon 51 skipping in the cynomolgus monkey with eteplirsen treatment

<i>Tissue</i>	<i>Average % Exon 51 Splicing ± 1 SD</i>				
	0 mg/kg IV	5 mg/kg IV	40 mg/kg IV	320 mg/kg IV	320 mg/kg SC
Quadriceps muscle	0.0 ± 0.0	0.5 ± 0.5	0.6 ± 0.3	8.2 ± 7.4	1.3 ± 0.5
Heart	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.2	4.5 ± 2.9	1.4 ± 0.5
Diaphragm	0.0 ± 0.0	0.2 ± 0.2	0.9 ± 0.7	6.1 ± 3.5	2.2 ± 0.9

SD standard deviation

Dr. Hawver also discusses that published studies present evidence for exon skipping and induction of dystrophin protein expression in mouse and dog DMD models using species-specific exon skipping phosphorodiamidate morpholino oligomer (PMOs), and often correlated these changes with reductions in muscle pathology and/or improvements in muscle function. In reference to the eteplirsen NDA, Dr. Hawver notes that the most robust finding among the studies provided or referenced is the wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles. Dr. Freed, Supervisory nonclinical reviewer, describes a clear dose-response in a study¹ in mdx and C57Bl that tested the effects of a mouse-specific PMO targeting exon 23. At the low dose, dystrophin-positive fibers were increased up to 5% of normal in skeletal muscle. The maximum amount of (truncated) dystrophin protein was 2.6% of normal, based on Western blot analysis. At the mid-dose, 10 to 50% fibers were dystrophin-positive were in skeletal muscle, and levels of dystrophin protein were up to 17.1% of normal (Western blot). The distribution of protein-positive fibers was reported to be highly variable among muscle groups in an individual animal and in the same muscle type among animals. Significant improvement in muscle function was observed. Further enhancement of exon skipping and muscle function was observed at the higher doses, e.g., with dystrophin-positive fibers close to 100%, and levels of dystrophin protein 25-50% of normal.

Another study discussed by Dr. Freed was conducted in mdx mice in order to address the issue of how much dystrophin is needed to protect muscles. In that study, higher acute doses of peptide-conjugated PMO were associated with dystrophin expression in the tibialis anterior at levels of 5-15% of wild type; none was detected at the lower acute doses. The authors concluded that 15% of wild type (“low level dystrophin restoration”) was sufficient to protect muscle (eccentric contraction-induced muscle damage) but not sufficient to “substantially” improve muscle function (maximum isometric force). The effects of repeated dosing (Q2W)

¹ Wu B et al. Mole Therap 19(3):576-583, 2011. The study was referenced by the applicant in the eteplirsen NDA.

on muscle pathology and function were also tested in tibialis anterior from mdx mouse. Western blot analysis indicated dystrophin expression around 50% of wild type, which positively correlated with maximal isometric force and reduced muscle pathology. Dr. Freed concludes that the applicant conducted only a minimal PD assessment of eteplirsen in animals, assessing exon skipping in muscles from a 12-week monkey study. Dr. Freed notes that the monkey study demonstrated dose-related increases in exon skipping. She also notes that published literature suggests that a minimum threshold for functional benefit or protection of muscle has not been identified, but that higher doses and/or longer duration may be associated with greater effects.

Dr. Hawver comments that pivotal toxicology studies of eteplirsen were conducted in male monkeys (39-week study) and juvenile male rats (10-week study), and that a 26-week study was conducted with a mouse-specific surrogate in male transgenic mdx mice. Dr. Hawver observes that the primary target organ of toxicity was the kidney in all three species, as evidenced by dose-dependent renal tubular cytoplasmic basophilia and/or vacuolation and, at the high dose, tubular degeneration/necrosis. Dr. Hawver also notes that in the mdx mouse study, dilatation of the lateral ventricles of the brain was observed at the mid and high doses. The mechanism of this effect and its relevance to humans is unknown. Dr. Freed believes that although toxicities were observed in mouse, juvenile rat, and monkey (kidney in all species; dilatation of lateral ventricles in mdx mouse; bone morphology in juvenile rat at all doses), the kidney toxicity was minimal and is monitorable and bone growth is monitorable in children. Dr. Freed notes that the dilatation of lateral ventricles is not monitorable and may be relevant to DMD patients, but was not thought to be of sufficient concern to halt clinical development. Dr. Freed notes that safety margins based on plasma exposures at the NOAELs are low (or non-existent in the case of bone) (<1 in mdx mouse, 3.4 in monkey), but observes that plasma exposures at the highest doses tested, which, with the exception of the moderate dilatation of lateral ventricles, were associated with minimal-to-slight toxicity were 17 and 20 times the anticipated human exposure. So, presuming that toxicities can be monitored in humans, Dr. Freed believes that nonclinical data would support doses >30 mg/kg in humans. Considering the seriousness of DMD, the unmet medical need, and the nature of the toxicities observed in animals, I believe that the nonclinical data would support, with proper monitoring, dosing in DMD patients at least up to 200 mg/kg, a dose expected to provide exposure similar to the most sensitive species NOAEL for the toxicities seen in animals. If the human safety experience at these doses is acceptable, further dose escalation is possible in DMD patients.

Dr. Hawver and Dr. Freed recommend that carcinogenicity studies in two species be conducted as a post-marketing requirement. I agree that for this serious indication with unmet need, carcinogenicity studies could be deferred to after marketing of the drug has started.

6. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) concludes that a relationship between eteplirsen dose and changes in 6-minute walk distance (6MWD) cannot be characterized based on the results of Study 201/202, and that comparison of changes in 6MWD and NSAA score between eteplirsen-treated patients and historical controls does not provide clear evidence of efficacy. As I will discuss later in this memo, I am in full agreement with those conclusions.

The Office of Clinical Pharmacology (OCP) further concludes that due to lack of clear evidence of benefit from eteplirsen in Study 201/202, and considering the pharmacokinetics of eteplirsen (3 to 4 hours plasma half-life, urinary excretion of 60-70% of the dose within 24 h post-dose), the applicant should evaluate doses greater than 50 mg/kg (administered weekly), or alternate regimens that would include loading and maintenance doses. As I discussed above, nonclinical data do support testing higher doses of eteplirsen in DMD patients, and I find the OCP recommendation fully justified, based on all nonclinical and clinical data generated to date for eteplirsen.

In their review of the pharmacokinetics of eteplirsen, the Office of Clinical Pharmacology observes that approximate dose-proportionality and linearity in PK properties were observed following multiple doses of eteplirsen. There was insignificant drug accumulation following weekly dosing across the dose range of 0.5 to ~50 mg/kg. Following single or multiple IV infusion, the peak plasma concentrations of eteplirsen occurred near the end of infusion, and plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline, with the majority of drug elimination occurring within 24 hours. Plasma protein binding of eteplirsen ranges between about 5 to 15%. Eteplirsen is metabolically stable in vitro, with no evidence of metabolism or metabolites. At 30 and 50 mg/kg weekly doses, urinary excretion accounts for about two thirds of the dose. Elimination half-life is about 3.5 hours. Inter-subject variability of eteplirsen PKs ranges between 20 and 55%.

The Office of Clinical Pharmacology expects eteplirsen to have a low potential for drug-drug interaction in human, based on results of in vitro investigation on microsomal metabolism, plasma protein binding, inhibition or induction of major CYP isozymes or major drug transporters at the concentration range studied for clinical dosing regimen.

7. Clinical Microbiology

Not applicable.

8. Clinical/Statistical-Efficacy

From a clinical and statistical perspective, a complete response action is recommended for NDA 206488 by all members of the efficacy review team: Dr. Breder, clinical reviewer, Dr. Farkas, Clinical Team Leader, and Dr. Yin, statistical reviewer. In addition, Dr. Atul Bhattaram, from OCP, played a key role in the evaluation of the efficacy database, and produced many of the graphs presented below. As discussed above, OCP also concluded that there is no clear evidence of efficacy of eteplirsen.

Clinical Development Program

As explained by the applicant, eteplirsen's intended mechanism of action is by removal of exon 51 of the pre-messenger ribonucleic acid (RNA), thereby restoring the messenger RNA "reading frame." This shift would enable the production of a truncated form of the dystrophin protein. By increasing the quantity of an abnormal, but potentially functional, dystrophin protein, the objective is to slow or prevent the progression of DMD.

To support the efficacy of eteplirsen, the applicant conducted two small exploratory studies (Study 28 and Study 33) to assess the potential for eteplirsen to increase expression of an altered mRNA and to increase dystrophin expression, and a single controlled clinical study (Study 201/202) in 12 patients to assess whether eteplirsen increased expression of dystrophin protein, leading to clinical benefit.

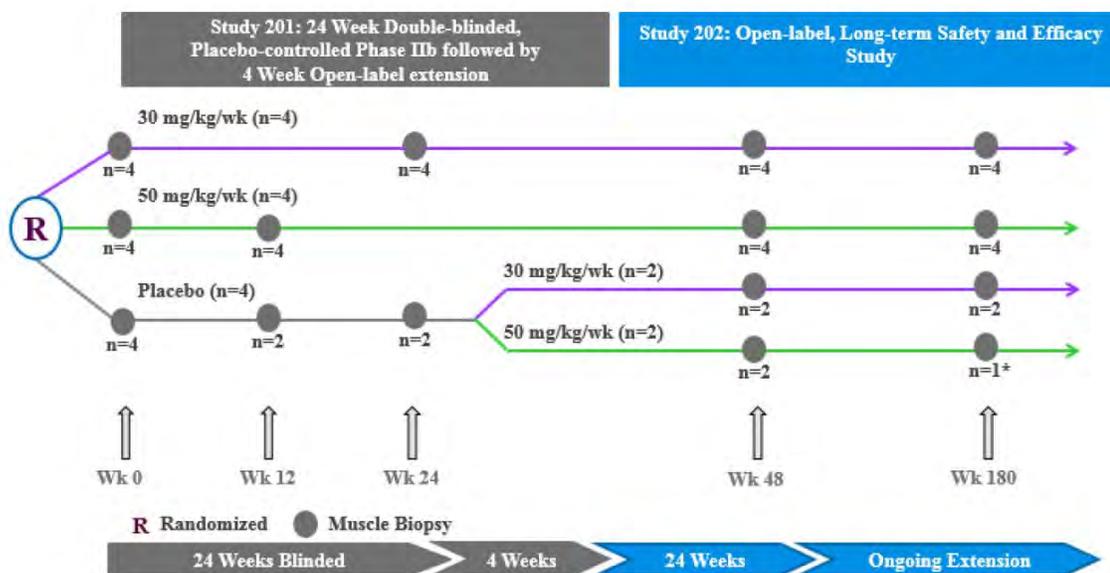
Study 33 was an exploratory study in which small doses of eteplirsen (up to 0.9 mg) were injected directly into a foot muscle in seven patients with DMD. The study showed a clear dose-response in mRNA expression and dystrophin production, with no effect at the initial dose tested, strongly supporting the importance of appropriate dose-finding. Also, as the drug was administered intramuscularly, it is very difficult to extrapolate what intravenous doses would be necessary to achieve similar intramuscular exposures to those obtained by direct injection in Study 33. The clear conclusion, though, is that adequate dose-finding is critical. Also, in Study 33, there was a ten-fold difference between the tested dose that led to pharmacodynamic activity and the dose that did not. As will be discussed below, there is less than a two-fold difference between the two eteplirsen doses tested in Study 201/202, and there is no information as to whether higher doses of eteplirsen administered intravenously may lead to levels of dystrophin expression as high as those reported in Study 33.

Study 28 was an exploratory study in which eteplirsen was administered intravenously once a week for 12 weeks at doses up to 20 mg/kg in 19 patients with DMD. As discussed by Dr. Breder, the applicant reported that across the 17 evaluable patients, the mean percentage of dystrophin-positive fibers increased from about 2% at baseline to up to 19% with the highest dose tested (20 mg/kg weekly). However, there was no clear dose-response, and the results appeared highly variable, with the 2 mg/kg weekly dose leading to a 12% absolute increase in

dystrophin positive fibers, while the 4 mg/kg weekly dose led to a decrease in the percentage of positive fibers. The study also had major methodological issues, similar to those discussed below for Study 201/202, and is overall inconclusive.

Study 201/202 was the only concurrently controlled clinical trial conducted by the applicant intended to assess a clinical endpoint. Study 201/202 (Figure 1) began as a 24-week randomized placebo-controlled study (Study 201) comparing three groups of four patients each, treated weekly with intravenous eteplirsen 50 mg/kg, eteplirsen 30 mg/kg, or placebo (the 4 placebo patients were divided in two subgroups, 2 patients switched to eteplirsen 30 mg/kg at Week 24, and 2 switched to eteplirsen 50 mg/kg at Week 24).

Figure 1: Design of Study 201/202 (copied from applicant’s Advisory Committee Briefing materials, page 51)



The prospectively planned primary endpoint of Study 201 was an assessment of dystrophin in skeletal muscle. In Study 201, all twelve patients had a muscle biopsy at baseline (*first biopsy*) and Week 48 (*third biopsy*). In addition, patients had a *second biopsy* either at Week 12 (50 mg/kg group) or Week 24 (30 mg/kg group). The randomized controlled phase (Study 201) was followed by an open-label extension phase (Study 202) in which patients continued to receive eteplirsen at the same dose as they did after Week 24 of Study 201, i.e., six patients on eteplirsen 30 mg/kg weekly, and six patients on 50 mg/kg weekly. Study 202 had a 6-Minute Walk Test (6MWT) at Week 48 as prespecified primary endpoint, but continued beyond Week 48, and is still ongoing at the time of writing this memo. In Study 202, 11 of the 12 patients had a *fourth biopsy* at Week 180 (~3.5 years).

After the first 3 biopsies were analyzed, FDA conducted an inspection of the facility which completed the biomarker analyses, and identified significant methodological issues, which cast

serious doubts on the reliability of assessments from the first three biopsies. These issues are discussed in detail by Dr. Rao in his review. In light of these concerns, FDA worked collaboratively with the applicant on methods for a reassessment of the images of the first three biopsies, as well as collection of additional data that could be more reliable. The goal of this effort was to help the applicant apply suitable, consistent, and objective methods for measuring dystrophin protein that would be amenable to independent verification for any future biopsies for patients in Study 201/202 and other planned studies. These improved methods were applied to the following:

- Week 180 biopsy
- Re-read of immunofluorescence images from the first three biopsies
- Re-do of immunofluorescence and Western blot analysis of the baseline samples for the three eteplirsen-treated patients who had archived pre-treatment muscle tissue².
- Immunofluorescence and Western blot analysis for six external untreated patients with DMD amenable to exon 51 skipping (i.e., patients who were not participants in Study 201/202). These external untreated patients and three baseline samples from eteplirsen-treated patients were compared with the treated week-180 samples from eleven treated patients together in the same experimental analyses.

It is important to note that Week 180 biopsies in eteplirsen-treated patients came from the deltoid, while biopsies for the external controls and preserved baseline muscle samples came from the biceps in all but one patients. As dystrophin expression is known to vary between muscles, this difference creates an additional source of variability in the study results.

Expression of the dystrophin messenger RNA in DMD patients muscle

The applicant evaluated the effect of eteplirsen on production of dystrophin messenger RNA in Study 33, Study 28, and Study 201/202. Skipping of the mRNA exon was assessed using reverse transcriptase polymerase chain reaction (RT-PCR), a standard technique commonly used in molecular biology laboratories to detect RNA expression. The PCR results of Study 33 showed an apparent dose-response in exon 51 skipping. As discussed by Dr. Rao, some baseline samples of Study 201 also showed a skipped mRNA band, likely due to revertant or trace dystrophin mRNA. Dr. Rao also observes that after eteplirsen-treatment, an appreciably pronounced band for the skipped mRNA was apparent in each of the 11 post-treatment samples of patients from Study 201. Dr. Rao also notes that the applicant's RT-PCR technique is not quantitative due to a lack of a reference gene. In addition, the presence of an exon skipped band does not indicate that the mRNA was translated into a functional protein.

² An important limitation of the re-do of immunofluorescence and Western blot s that tissue (and protein) for the 3 patients who had preserved (frozen) baseline samples is that degradation of proteins is known to occur over time, and the effect that extended freezing of the sample samples had on dystrophin results is impossible to quantify.

Therefore, this biomarker provides little support of efficacy for eteplirsen; it does, however, provide evidence that eteplirsen causes at least some degree of exon 51 skipping, as intended.

Production of Dystrophin Protein in Muscle

The applicant evaluated the effect of eteplirsen on dystrophin expression primarily in Study 201/202, but also in Study 28 and Study 33. Production of dystrophin was assessed by two different methods: immunofluorescence (IF) and Western blot. In considering these two measures, it is important to note that Western blot is considered to be a quantitative method, whereas immunofluorescence is generally considered to be less quantitative, and is more often relied upon to show the localization of protein in tissue sections. The applicant used Western blot to quantify dystrophin protein. Immunofluorescence methods were used to distinguish “positive” muscle fibers, i.e., those with at least some degree of positivity, from “negative” muscle fibers in tissue biopsy sections, and the data were also analyzed based on the staining intensity of identified areas of tissue sections. I discussed above the dystrophin expression results of Study 28 and 33. I will now review the dystrophin expression results for Study 201/202.

Immunofluorescence (IF)

The immunofluorescence technique can be used to look at the percentage of dystrophin-positive fibers, and at the levels of dystrophin intensity per fiber. As discussed by Dr. Farkas, the applicant’s definition of a positive fiber was not based on a threshold amount of dystrophin or staining brightness, but rather only on “a majority of the fiber perimeter stain at an intensity judged by eye to be above background of the image.” Consequently, “17% positive fibers” does not correspond to 17% of normal dystrophin levels, or to 17% of fibers being as bright as in BMD. The percent positive fiber result is, instead, mainly useful for localization of dystrophin, not quantification.

Percentage of dystrophin positive fibers

The percentage of dystrophin-positive fibers in tissue obtained from muscle biopsies was the prospectively planned primary endpoint of Study 201. Substantial increases in dystrophin in Study 201 were initially reported in a publication,³ which stated the “...percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively....)”. However, as discussed above, there were technical problems with the initial analyses of the first three biopsies, and the biopsies were reanalyzed by three blinded readers. It is important to note that this reanalysis, as

³ *Ann Neurol* 2013;74:637

discussed by Dr. Rao and Dr. Farkas, does not address all of the methodological issues that were identified, and still has significant interpretability concerns.⁴

With these limitations in mind, on re-analysis of the first three biopsies by the three blinded readers, the changes in percent of positive fibers were considerably lower than those initially reported in the Nationwide Children's Hospital analysis, and also were inconsistent between the treatment groups, as illustrated in Table 2. For example, for the patients who were started on eteplirsen 50 mg/kg weekly from the beginning of Study 201, the mean percent dystrophin-positive fibers had an apparent modest increase, from 15% at baseline to 17% at Week 12, and to 25% at Week 48. However, for patients initially on placebo and switched to eteplirsen 50 mg/kg weekly at Week 24, there was no increase noted in the percent dystrophin-positive fibers between baseline and Week 48. As these patients, by Week 48, had received 24 weeks of treatment with eteplirsen, the results can directly be compared with the first 24 weeks of treatment in patients who immediately received eteplirsen treatment in Study 201. The discrepancy is obvious, and adds to the multiple concerns noted about the robustness and interpretability of the dystrophin data in Study 201/202. Of note, the change from baseline in percent of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry was the primary endpoint of Study 201. As noted by Dr. Ling, statistical reviewer, there was no statistically significant difference between the 50 mg/kg eteplirsen group and placebo at Week 12 ($p = 0.958$). At Week 24, the mean percentage of dystrophin positive muscle fibers was higher in the eteplirsen 30 mg/kg group than the placebo. However, the nominal p-value (0.002) for the comparison between eteplirsen 30 mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type-1 error due to multiple comparisons, and because the other primary endpoint comparison between the 50 mg/kg group and placebo was negative.

⁴ For example, Week 48 samples were processed separately for dystrophin immunofluorescence from earlier samples, and had higher background staining. As a consequence, valid comparison is not possible with earlier time points for percent positive fibers or total immunofluorescence because the higher background staining, and not necessarily an effect of drug, could be responsible for any differences observed.

Table 2: Study 201 immunofluorescence results for first three muscle biopsies (% positive fibers)

	Nationwide Children’s Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180
30 mg/kg (n=4)	18		41	70	14		27	23	17
50 mg/kg (n=4)	11	12		54	15	17		25	
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

For the eleven eteplirsen-treated patients who had a biopsy at Week 180, the three blinded veterinary pathologists reported a mean of 17% of dystrophin-positive fibers for the eteplirsen-treated patients, a level considerably lower than reported by Nationwide Children’s Hospital for the first three biopsies.³ Week 180 biopsies were also compared with untreated controls (i.e., preserved baseline tissues of three eteplirsen-treated patients and the six external controls). The untreated control patients were reported as having about 1% dystrophin-positive fibers. For the three eteplirsen-treated patients who had retained baseline samples, the proportion of dystrophin-positive fibers upon reanalysis respectively was 1.1%, 2.6%, and 0.2% of normal. This contrasts with original baselines values, respectively, of 11.7%, 17%, and 18.9%. As discussed by Dr. Breder, the basis for the differences in the percent positive fibers from the time they were originally stained and the time of the 4th biopsy is not known; however, because they were stained with the same antibody and nearly the same procedure, one would expect the levels to be similar. One factor which is concerning to Dr. Breder, and to me, is that the tissue for the fiber staining as well as the other biomarker assays had been in the freezer for about 3 years. Without a method to control for or evaluate the potential loss of immunoreactivity, the protein may have undergone changes which would result in a lesser level in the biomarker assays. For the two patients with retained baseline muscle samples who also had a biopsy at Week 180 (Patient 013 and Patient 015), the proportion of dystrophin-positive fibers at Week 180 respectively was 19.1%, and 18.5%. This number contrasts with

baseline values in eteplirsen-treated patients (as reanalyzed by the three blinded readers), ranging between 10 and 15% of fibers; it is unclear what role differences between the analytical methods, or other factors, such as a difference in muscle sampled, or protein degradation over time, played in the discrepant results. Also, the data were analyzed in a single laboratory, fraught with methodological issues during the development program and have not been independently substantiated.

Levels of dystrophin intensity per fiber (“Bioquant”)

As discussed by Dr. Breder and by Dr. Rao, after breaking the blinding code, the applicant discarded their original analysis, as according to the applicant, this magnification did not “allow for optimal differentiation of the muscle fibers for quantitation”. It is important to note that this original analysis was negative, while the post hoc analysis conducted by the applicant shows some numerical increases in the average fiber intensity in the eteplirsen treatment group, compared with placebo. As noted by Dr. Rao, dismissing the original analysis is not good scientific practice.

For the fourth biopsy, the applicant reported that the muscle biopsy from Week 180 displayed a statistically significant increase in the relative associated fluorescence intensity. The mean relative fluorescence value for treated patients was reported as 22.6 versus 9.4 for the untreated control samples, which came from a population of six untreated DMD boys, and the baseline biopsy from three of the original eteplirsen treated patients. An important limitation of the Week 180 Bioquant analysis is that there were no matched controls from the same patients and same muscle groups for all treated samples. As discussed by Dr. Breder, it is not clear how similar the external controls were to the treated patients, and it is not clear that the applicant selected the external controls completely at random, i.e., bias may have been introduced.

Overall, the immunofluorescence data do not provide consistent evidence that the percent of dystrophin positive fibers may have increased as a result of eteplirsen treatment. The issues described above deeply affect the interpretability of the findings, and make any quantification of the changes unreliable. In addition, as analyses based on immunofluorescence overestimate the amount of dystrophin in tissue sections because a muscle fiber can be considered “positive” if it exhibits any staining at all, the percent dystrophin-positive fibers by immunofluorescence is not the most meaningful way to estimate dystrophin content. The Western blot analyses are informative for that purpose.

Western Blot

The applicant provided a second line of evidence, Western blot analysis, to support the concept that eteplirsen increases dystrophin production in skeletal muscle. As discussed by Dr. Rao, the Western blots from the first 3 biopsies had oversaturated bands, did not have appropriate

controls or quality control metrics and were essentially uninterpretable. Therefore, the results of Western blot analyses for the first three biopsies do not merit discussion in this memo.

As discussed by Dr. Rao, the methodologies used by the applicant were relatively improved for the 4th biopsy. The applicant, however, used a different antibody (Dys 1) for the fourth biopsy Western blots, potentially confounding comparisons to the patients' original pre-treatment baseline values (which were assessed with Mandys106 antibody in all but one patients). As the Western blot assessments prior to Week 180 were essentially uninterpretable, and used a different antibody, FDA suggested that the applicant attempt reassessing baseline dystrophin levels, i.e., pre-treatment, for patients who had available baseline muscle samples, together with the Week 180 samples. Of the three patients who had retained baseline samples, only two also had a biopsy at Week 180: Patient 13, and Patient 15 (presented in Table 4). In that reassessment on the retained sample which had been frozen for about 3 years, both of these patients had baseline dystrophin levels below the level of quantification, i.e., below 0.25%. As for immunofluorescence analyses, data from external controls were used to supplement the limited baseline samples that were available for re-analysis. When all of the untreated and baseline samples are considered, the applicant reports a value of dystrophin level of 0.08% of normal in controls.

There are, however, important limitations with respect to interpretation of the results of these controls. We already discussed that Week 180 biopsies in eteplirsen-treated patients were obtained from the deltoid, while control biopsies came from the biceps in all but one patient, for whom the biopsy also came from the deltoid. As discussed by Dr. Farkas, the deltoid is one of the few muscle groups that, along with the calf muscle, can be hypertrophied in DMD. It is not clear to what extent differences in dystrophin expression between muscle groups may have contributed to the change in dystrophin reported for the 4th biopsy. Also, as discussed by Dr. Breder, the untreated DMD controls used in the fourth biopsy analyses were not necessarily selected at random from a representative patient population, as they came from patients from the ongoing eteplirsen Phase 3 confirmatory study 4658-301. Finally, the tissue was not of comparable quality (i.e., fresh versus frozen for about 3 years) for Week 180 biopsies vs. those of controls. Because of these issues, Dr. Rao concluded that it is not clear exactly how much dystrophin, if any, was made based on a drug effect at the time of the fourth biopsy.

Notwithstanding these critical limitations, by Western blot, the most accurate quantitative method used by the applicant, the mean dystrophin level after about 3.5 years of eteplirsen treatment (at Week 180) was 0.93%. Table 3, adapted from the applicant's submission, shows the results for dystrophin quantification from the fourth biopsy for the eleven patients who consented to muscle biopsies at Week 180. Most patients had two separate Western Blot estimates, and the values were averaged to provide the final results. It is also noteworthy that three of the patients had a variability of 0.7% or greater between their measurements. Also,

there was a poor correlation between immunofluorescence and Western blot data.

Table 3: Applicant’s Quantification of Dystrophin by Western Blot at Week 180 (% of normal)

Subject	Test 1 (%)	Test 2 (%)	Mean	Intra-Patient variability
002	0	0.28	0.14	0.28
003	0 0	0	0	0
004	1.22	0.69	0.955	0.53
006	2.83	2.11	2.47	0.72
007	0	0	0	0
008	0.93	1.02	0.975	0.09
009	0.58	0.46	0.52	0.12
010	1.45	1.78	1.615	0.33
012	0.75	0	0.375	0.75
013	1.15		1.15	-
015	2.43	1.67	2.05	0.76

Because of the limitations in controls used to interpret Week 180 dystrophin findings, it was not clear exactly how much dystrophin, or even if any dystrophin at all, was made in response to the drug. As additional muscle biopsies at baseline and after 48 weeks of eteplirsen treatment were available in an ongoing eteplirsen study (“PROMOVI Study⁵”), the applicant was asked to analyze these samples and submit the results in order to provide substantiation of the dystrophin findings of Study 201/202. Western blots were conducted on samples from 13 patients treated with eteplirsen 30 mg/kg/week for 48 weeks. The Western blot methods used for these additional analyses were generally similar to those used for the Week 180 muscle samples from Study 201/202. Twelve of the 13 patients had paired biceps biopsies, and a

⁵ The PROMOVI study is an open-label, multi-center, 96-Week study of eteplirsen in patients with mutations amenable to exon 51 skipping compared with a concurrent untreated control arm composed of patients not amenable to exon 51 skipping

single patient had paired triceps biopsies. Results are available for 12 out of the 13 patients, as both gels for one patient failed acceptance criteria. Table 4, Table 5, and Table 6 summarize the Western blot results. Dystrophin levels that were below the level of quantification (0.25% of normal) were imputed as 0.24% in Table 4, imputed as zero in Table 5, or presented as the observed value in Table 6. Of note, actual values under 0.25% may represent less accurate estimates, because of the validation cutoffs (0.25% to 4%) for the assay, but still represent actual values that can be used to estimate the treatment effect, while keeping in mind the lower accuracy of these values. On the other hand, considering all values under 0.25% as zero introduces a greater imprecision, and magnifies changes from baseline if the actual value is greater than zero percent. Regardless of the method of imputation of baseline dystrophin data, there was a statistically significant difference in dystrophin levels between baseline and Week 48. The magnitude of the effect, however, is very small, in the order of 0.3% of normal values, on average.

Table 4: Western Blot results in boys from the Promovi Study (levels below level of quantification imputed as 0.24%)

	Baseline	Week 48	Change From Baseline	Fold Change From Baseline
n	12	12	12	12
Mean (% Dystrophin)	0.260	0.478	0.218	1.915
SD (SE)	0.0469 (0.0135)	0.4066 (0.1174)	0.4173 (0.1205)	1.7331 (0.5003)
Median	0.240	0.330	-0.018	1.066
Min, Max	0.24, 0.37	0.24, 1.57	-0.07, 1.33	0.81, 6.54
			P = 0.041	

Table 5: Western Blot results in boys from the Promovi Study (levels below level of quantification imputed as 0%)

	Baseline	Week 48	Change From Baseline	Fold Change From Baseline
n	12	12	12	12
Mean (% Dystrophin)	0.060	0.378	0.318	3229.320
SD (SE)	0.1402 (0.0405)	0.4760 (0.1374)	0.5026 (0.1451)	4986.0753 (1439.3560)
Median	0.000	0.275	-0.078	725.514
Min, Max	0.00, 0.37	0.00, 1.57	-0.07, 1.57	0.00, 15700.00
			P = 0.023	

Table 6: Western Blot results in boys from the Promovi Study (actual values)

	Baseline	Week 48	Change From Baseline	Fold Change From Baseline
n	12	12	12	12
Mean (% dystrophin)	0.157	0.440	0.283	3.723
SD (SE)	0.1159 (0.0335)	0.4341 (0.1253)	0.4153 (0.1199)	3.0189 (0.8715)
Median	0.150	0.330	0.098	2.485
Min, Max	0.02, 0.37	0.09, 1.57	-0.07, 1.33	0.81, 10.44
			P = 0.008	

Individual dystrophin results for the “PROMOVI” patients are presented in Table 7.

Table 7: Individual Western Blot results in boys from the Promovi Study

SR-CR-16-003 Patient WB Analysis
4658-301 Week 48 Interim Analysis

June 27, 2016

Listing 1.1
Western Blot Results
Values < 0.25 Treated as Reported

Western Blot Analysis

Dummy ID	Time Point	Image Filename	Gel #	Blinded Sample ID	Pass/Fail	Calculated % Dystrophin	Average Value	Change from Baseline	Fold Change
301-01	Baseline	SR-CR-16-003_GEL#1_DYS1_30MIN.TIF	1	FORD-22559	PASS	0.15	0.13		
	Week 48	SR-CR-16-003_GEL#2_DYS1_30MIN.TIF	2	FORD-22559	PASS	0.11	0.26	0.13	1.96
301-02	Baseline	SR-CR-16-003_GEL#3_DYS1_30MIN.TIF	3	CHEVY-27336	PASS	0.35	0.35		
	Week 48	SR-CR-16-003_GEL#4_DYS1_30MIN.TIF	4	CHEVY-27336	FAIL	0.26	0.36	0.01	1.03
301-03	Baseline	SR-CR-16-003_GEL#5_DYS1_30MIN.TIF	5	FORD-24422	PASS	0.06	0.06		
	Week 48	SR-CR-16-003_GEL#6_DYS1_30MIN.TIF	6	FORD-24422	PASS	0.06	0.37	0.31	6.17
301-04	Baseline	SR-CR-16-003_GEL#7_DYS1_30MIN.TIF	7	FORD-27138	PASS	0.04	0.04		
	Week 48	SR-CR-16-003_GEL#8_DYS1_30MIN.TIF	8	FORD-27138	FAIL	0.06	0.10	0.06	2.50
301-05	Baseline	SR-CR-16-003_GEL#9_DYS1_30MIN.TIF	9	FORD-28500	FAIL	0.10	0.17		
	Week 48	SR-CR-16-003_GEL#10_DYS1_30MIN.TIF	10	FORD-28500	PASS	0.17	1.02	0.85	6.00
301-06	Baseline	SR-CR-16-003_GEL#11_DYS1_30MIN.TIF	11	CHEVY-24986	PASS	0.37	0.37		
	Week 48	SR-CR-16-003_GEL#12_DYS1_30MIN.TIF	12	CHEVY-24986	FAIL	0.46	0.30	-0.07	0.81
301-07	Baseline	SR-CR-16-003_GEL#13_DYS1_15MIN.TIF	13	FORD-20841	FAIL	0.04	0.17		
		SR-CR-16-003_GEL#14_DYS1_15MIN.TIF	14	FORD-20841	PASS	0.17			

Note: For calculation of Fold Change, baseline values of 0 were imputed as 0.0001.
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