

## VIEWPOINT

# Approving a Problematic Muscular Dystrophy Drug Implications for FDA Policy

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**In September 2016**, the US Food and Drug Administration (FDA) approved eteplirsen (Exondys 51), a new drug for Duchenne muscular dystrophy (DMD), overruling the recommendations of both its scientific staff and its external advisory committee. Duchenne muscular dystrophy is a progressive X-linked genetic disease caused by mutations in a gene that produces the protein dystrophin that helps stabilize muscle fibers. It is usually fatal by the third decade of life. No disease-modifying treatments are available.

Eteplirsen offered a promising new therapeutic approach that would correct a mutation in a gene coding for dystrophin, allowing production of a truncated but functional version of the protein. In particular, eteplirsen was designed to skip exon 51, which would address the mutations in about 10% to 15% of patients with DMD (an estimated 2000-2500 cases in the United States). Despite this innovative mechanism, the development of eteplirsen was controversial, starting with its manufacturer-supported pivotal double-blind study, which involved only 12 patients: 8 were randomized to 2 different eteplirsen doses and 4 were randomized to placebo for 24 weeks. The latter were then switched to eteplirsen and all were to be followed for an additional 24 weeks. The sample size was substantially smaller than the study sample size in which a similar DMD drug, drisapersen, had been tested in 3 randomized trials that together enrolled 290 patients. The FDA declined to approve drisapersen in 2015 after these studies showed no clear benefit after 24 weeks in prespecified clinical end points, such as changes in a 6-minute walk test. Those trials also suggested the possibility of safety problems, including renal toxic effects and thrombocytopenia.

In the eteplirsen study, by contrast, the primary trial end point was a surrogate measure: an increase in the presence of dystrophin in muscle biopsy specimens. Serial biopsies were performed at 12, 24, and 48 weeks, although biopsies were performed on only half the treated patients at each of the 12- and 24-week periods; all 12 patients were receiving drug treatment by week 48. The biopsy specimens were analyzed by scientists blinded to the patients' group assignments but not blinded to the time receiving treatment.<sup>1</sup> In a 2013 publication, the authors reported increases to about 50% of normal in dystrophin-containing fibers in the biopsy specimens,<sup>2</sup> results that were met with enthusiasm by the DMD community. However, these results were based on an immunohistochemical assay that assessed only an increase of newly produced dystrophin compared with baseline values. Quantitative Western blot analysis of a fourth biopsy performed in 11 of the study patients after 3 to 3.5 years of continued open-label extension showed an actual increase to only a mean (SD) of 0.9% (0.8%) of normal dystrophin levels, far less than what might be expected to pro-

vide clinical benefit. A more rigorous, fully blinded reanalysis of the immunohistochemical assay organized by the FDA cast further doubt on the initial results.<sup>3</sup>

The trial also assessed clinical progression. At 24 and 48 weeks, there was no consistent advantage in the 6-minute walk test capacity of patients who received eteplirsen compared with those initially given placebo. However, new post hoc calculations excluded 2 eteplirsen-treated patients who deteriorated quickly while receiving therapy; these analyses suggested a statistically significant advantage for the remaining treated patients. These more selective post hoc analyses were highlighted in the figure displaying this finding in the 2013 article<sup>2</sup> and in the manufacturer's press release announcing the success of the trial.<sup>4</sup> Subsequent evaluation of 6-minute walk test data over 3 to 3.5 years of open-label therapy appeared to be associated with slower rates of decline when compared with a historical cohort, but the problematic nature of historical controls complicated the interpretation.

Controversy over eteplirsen came into broader public view when the FDA convened an advisory committee in April 2016 to review these data. That hearing included more than a thousand public attendees and more than 4 hours of comments from patients, families, advocates, scientists, and legislators. The public presentations were frequently emotional, and nearly all of the presenters (51 of 52) favored drug approval. The advisory committee was generally unimpressed with the efficacy data, although the committee split its vote: 7 members found no evidence that eteplirsen was clinically effective in treating DMD (vs 3 in favor and 3 abstentions), and 7 members found that the drug did not produce dystrophin at a level likely to result in clinical benefit (vs 6 in favor).

After the meeting, the FDA delayed its decision and requested additional data, including Western blot assays from biopsy specimens in 13 patients from another ongoing study at week 48. These data showed a mean increase in dystrophin to just 0.2% to 0.3% of normal. In September 2016, another reason for the delay was revealed—disagreement within the FDA about the approval decision. The main FDA scientific reviewers all opposed approval, but Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, overruled them, suggesting that the extremely small increase in dystrophin might conceivably translate to clinical benefit.<sup>1</sup> She indicated that considering the life-threatening nature of the disease and the lack of reasonable alternative treatments, the FDA should exercise "the greatest flexibility possible" under its statutory authority in considering eteplirsen's efficacy.<sup>1</sup> The internal FDA review staff took the unusual step of appealing to Commissioner Robert Califf, MD, who upheld Woodcock's decision.<sup>1</sup>

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The drug was thus approved, and the manufacturer was told to conduct a randomized trial to “verify [sic] the clinical benefit of eteplirsen,”<sup>5</sup> with a deadline of May 2021 for submission of its results. A placebo group was not required (although it would be difficult to recruit patients to a placebo-controlled trial of an approved drug), and accordingly, without a true control, it is not clear how the results regarding drug efficacy will be assessed. Barring a major unexpected safety problem, it is unlikely that the new study could provide sufficient evidence leading to removing eteplirsen from the market.

Eteplirsen represents another case in which the FDA used a surrogate measure (in this case muscle dystrophin levels) as the basis for approval. However, the accelerated approval pathway through which eteplirsen was authorized requires that a surrogate end point must be reasonably likely to predict clinical benefit of the drug,<sup>6</sup> and this standard is challenged by the minimal changes seen in the dystrophin levels. Speeding drugs to market based on such biomarker outcomes can actually lead to a worse outcome for patients, even those with life-threatening diseases, if a product confers no meaningful benefit and carries a risk of adverse effects and a high cost. Immediately after approval, the manufacturer announced a price of \$300 000 per year for eteplirsen.<sup>7</sup> This approach also unfairly penalizes manufacturers that pursue a more rigorous course of development using more clinically relevant end points, while rewarding competitors that submit trials that have less evidence supporting efficacy.

The eteplirsen case also raises questions about how to integrate subjective and anecdotal patient experience in the FDA review process. Patient-reported clinical outcomes such as functional status can be of value in drug assessment. For pain, functional incapacity, or depression, patient-reported measures may even be the most important assessments of efficacy. However, such outcomes can be misleading in very small, poorly controlled, or un-

blinded studies that do not account for placebo effects. Similarly, the voices of patient advocates should be made known, but many such groups are financially supported by drug manufacturers to help advance their goals.<sup>8</sup> Even in the absence of such support, popular opinion can be shaped by uncritical enthusiasm by patients and their families, or by unbalanced reports from the manufacturer.

With the growth of pharmacogenetics and the current enthusiasm for “precision medicine,” more and more drugs are likely to be developed that alter laboratory tests or protein expression and are then tested in trials which assess such surrogate measures but which do not show convincing clinical outcomes. Approval by the FDA on this basis will apply enormous pressure on public and private payers to cover the very high prices of these drugs and will impose substantial cost burdens on uninsured or underinsured patients. (Since approval, at least 1 commercial insurer has declined to cover eteplirsen for its patients with DMD.) Meanwhile, more rigorous data from follow-up trials may be years away, or may never become available. This will further increase the nation’s growing expenditures for medications, even in the absence of clear patient benefit.<sup>9</sup>

One partial solution could be the adoption of novel regulatory models, such as limited approval with intensive collection of new clinical evidence, before a drug becomes universally available. As a further step, drugs that have not yet shown clinical outcome benefit could be made available at just the cost of production, or most profits could be kept in escrow, until adequate trials are completed.

Patients with DMD need better treatments, and drugs like eteplirsen might one day fill that role. For now, though, the drug 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.

#### ARTICLE INFORMATION

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#### REFERENCES

- Center for Drug Evaluation and Research, US Food and Drug Administration. Application number 206488Orig1s000: summary review. September 16, 2016. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/206488\\_summary%20review\\_Redacted.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf). Accessed October 3, 2016.
- Mendell JR, Rodino-Klapac LR, Sahenk Z, et al; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-647.
- US Food and Drug Administration. US Food and Drug Administration presentations for the April 25, 2016, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM500821.pdf>. Accessed October 3, 2016.
- Sarepta Therapeutics. Sarepta Therapeutics announces publication of eteplirsen clinical study results in the *Annals of Neurology* [news release]. Cambridge, MA: Sarepta Therapeutics; August 8, 2013. <http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1846052>. Accessed October 3, 2016.
- US Food and Drug Administration. Eteplirsen approval letter. September 19, 2016. [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2016/206488Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206488Orig1s000ltr.pdf). Accessed October 3, 2016.
- Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category—implications for patients. *N Engl J Med*. 2014;370(13):1252-1258.
- Silverman E. Sarepta to charge \$300K for Duchenne drug. “We tried to be reasonable,” CEO says. *Stat News*. September 19, 2016. <https://www.statnews.com/pharmalot/2016/09/19/sarepta-duchenne-drug-prices/>. Accessed October 3, 2016.
- Thomas K. Furor over drug prices puts patient advocacy groups in bind. *New York Times*. September 27, 2016. [http://www.nytimes.com/2016/09/28/business/furor-over-drug-prices-puts-patient-advocacy-groups-in-bind.html?\\_r=0](http://www.nytimes.com/2016/09/28/business/furor-over-drug-prices-puts-patient-advocacy-groups-in-bind.html?_r=0). Accessed October 3, 2016.
- Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA*. 2016;316(8):858-871.