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Mehul Bhattacharyya, Larry E Miller, Anna L. Miller & Ruemon Bhattacharyya

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EDITORIAL

The FDA approval of delandistrogene moxeparvovec-rokl for Duchenne muscular dystrophy: a critical examination of the evidence and regulatory process

Mehul Bhattacharyya[a], Larry E Miller [b], Anna L. Miller[b] and Ruemon Bhattacharyya[c]

[a]Department of Data Science, Arizona State University, Tempe, AZ, USA; [b]Department of Biostatistics, Miller Scientific, Johnson City, TN, USA; [c]Department of Public Affairs, University of California Los Angeles, Los Angeles, CA, USA

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The recent US Food and Drug Administration (FDA) decision to expand approval for delandistrogene moxeparvovec (delandistrogene moxeparvovec-rokl; Elevidys) in the treatment of Duchenne muscular dystrophy (DMD) [1] has ignited significant controversy within the medical and regulatory communities. This gene therapy received traditional approval for ambulatory patients aged 4 years and older, and accelerated approval for non-ambulatory patients in the same age group. However, this decision was made despite the drug failing to meet its primary endpoint in a pivotal Phase III clinical trial and against the recommendations of multiple FDA review teams and directors [2–4]. The approval raises serious questions about the integrity of the regulatory process and the strength of evidence required for drug approvals, particularly in rare diseases with high unmet medical needs.

DMD is a rare, X-linked genetic disorder affecting approximately 7 in 100,000 male births [5]. The disease is characterized by progressive muscle weakness due to mutations in the dystrophin gene, leading to the absence or deficiency of the dystrophin protein crucial for muscle fiber integrity [6]. While the devastating nature of DMD and the urgent need for effective therapies may have influenced the FDA decision, examining the available data raises significant questions about whether delandistrogene moxeparvovec provides substantial clinical benefits to justify its approval across such a broad patient population.

The primary evidence for delandistrogene moxeparvovec's efficacy comes from Study SRP-9001-301 (Study 301), a randomized, double-blind, placebo-controlled trial involving 120 male, ambulatory DMD patients aged 4–8 years. The primary endpoint of the study was the change in North Star Ambulatory Assessment (NSAA) total score from baseline to Week 52. Importantly, Study 301 failed to demonstrate a statistically significant difference between the delandistrogene moxeparvovec and placebo groups in this primary outcome measure. The least-squares mean change in NSAA total score was 2.57 (95% CI: 1.80, 3.34) for delandistrogene moxeparvovec versus 1.92 (95% CI: 1.14, 2.70) for placebo, resulting in a non-significant difference of 0.65 points (95% CI: −0.45, 1.74; $p = 0.24$). This failure to meet the primary endpoint is particularly concerning given that Study 301 was designed as a confirmatory trial following the drug's initial accelerated approval in June 2023 for ambulatory patients aged 4 through 5 years [7]. The earlier approval was based on the surrogate endpoint of micro-dystrophin expression at Week 12, with the expectation that clinical benefit would be verified in subsequent trials. The inability of Study 301 to demonstrate this benefit casts doubt on the validity of micro-dystrophin expression as a surrogate endpoint predictive of clinical improvement.

Proponents of the approval point to secondary endpoints and subgroup analyses that showed some improvements in functional measures [8]. For instance, the time to rise from floor test showed a least-squares mean change of −0.27 s for delandistrogene moxeparvovec compared to 0.37 s for placebo, resulting in a difference of −0.64 s (95% CI: −1.06, −0.23). Similarly, the 10-m walk/run test showed a difference of −0.42 s (95% CI: −0.71, −0.13) favoring delandistrogene moxeparvovec. However, these analyses were not adjusted for multiple comparisons, significantly increasing the risk of Type I error. As noted in the Office of Clinical Evaluation Director's memo, 'Given the exploratory nature of these analyses, they are considered potentially hypothesis-generating, but the results do not constitute substantial evidence of effectiveness due to the high likelihood that observed differences between the treatment groups may be due to chance' [4].

Given the paucity of data in the latter group, the FDA decision to grant traditional approval for ambulatory patients and accelerated approval for non-ambulatory patients is particularly puzzling. The Biologics License Application included data from only eight non-ambulatory patients in an open-label, single-arm study (SRP-9001-103), which is inadequate for drawing meaningful conclusions about efficacy in this population. The approval decision not only extrapolates potential benefits to patients without controlled clinical data but also potentially overlooks increased risks in the non-ambulatory population. Total viral dose, dependent on weight-based dosing, is considered a risk factor for complement-mediated pathologies like thrombotic microangiopathy in gene therapies [9]. Non-ambulatory patients, who are often

CONTACT Larry E Miller larry@millerscientific.com Department of Biostatistics, Miller Scientific, 3101 Browns Mill Road, Ste. 6, #311, Johnson City, TN 37604, USA

older and heavier, could face higher risks due to increased viral doses. This highlights the inadequacy of the current evidence base for approving delandistrogene moxeparvovec in this population.

Furthermore, the correlation between micro-dystrophin expression and functional outcomes remains uncertain. In Study 301, micro-dystrophin expression data were available for only 25% of patients, with the delandistrogene moxeparvovec group showing a mean change from baseline of 34% (SD: 41%) compared to 0% in the placebo group. The wide variability in delandistrogene moxeparvovec -induced micro-dystrophin expression is concerning. Exploratory analyses of micro-dystrophin expression and physical function outcomes (NSAA and Performance of Upper Limb 2.0) in Studies 301 and 103 showed a negative trend, but sample size limitations and study design issues preclude definitive conclusions.

The FDA's decision to approve delandistrogene moxeparvovec broadly despite these significant limitations in the evidence base raises serious concerns about the agency's adherence to its own standards for substantial evidence of effectiveness. The overruling of multiple review teams' recommendations for a Complete Response letter by the CBER Director undermines confidence in the FDA's rigorous review process and may set a dangerous precedent for future drug approvals.

Advocates for the approval argue that the urgent unmet need in DMD justifies a more flexible approach to evidence standards. They point to the devastating nature of the disease and the lack of effective treatments as reasons to expedite access to potentially beneficial therapies. Additionally, they argue that the positive trends in some secondary endpoints and subgroup analyses, particularly in younger patients, suggest a potential benefit that warrants further exploration in real-world settings. However, while the severity of DMD and the lack of effective treatments are undeniable, lowering the bar for approval risks exposing patients to potentially ineffective or even harmful therapies. Moreover, it may discourage the development of truly effective treatments by setting a precedent that incomplete or inconclusive data is sufficient for approval in rare diseases. Additionally, treating patients with adeno-associated virus vector therapy may preclude them from future, potentially more effective gene therapies due to the development of neutralizing antibodies against the viral vector. This 'one-shot' nature of current gene therapies should be an important consideration in the approval process. Furthermore, with a list price exceeding $3 million per treatment, the approval of delandistrogene moxeparvovec without robust evidence of efficacy raises significant concerns about resource allocation and opportunity costs for patients, insurers, and healthcare systems.

The approval of delandistrogene moxeparvovec also raises important questions about the accelerated approval pathway. This pathway is intended to provide earlier access to promising therapies for serious conditions based on surrogate endpoints, with the requirement that clinical benefit be verified in post-approval studies [10]. However, when confirmatory trials fail to demonstrate benefit, as in the case of delandistrogene moxeparvovec, the FDA must take appropriate action to protect public health and maintain the integrity of the approval process. It is worth noting that eteplirsen, another DMD therapy approved under the accelerated pathway in 2016, has yet to be converted to traditional approval due to lack of confirmatory data submission. The approval process for delandistrogene moxeparvovec bears striking similarities to that of eteplirsen. In both cases, senior FDA officials overrode internal reviewers to grant approval, a decision that sparked considerable controversy [11]. This pattern raises serious questions about the consistent application of regulatory standards and highlights potentially concerning trends in how the accelerated approval pathway is being utilized for rare diseases, where the urgency of unmet medical needs may be prioritized over robust evidence of efficacy.

The decision to approve delandistrogene moxeparvovec also appears to contradict the FDA's guidance on developing drugs for DMD [12]. This guidance emphasizes the importance of demonstrating clinically meaningful benefits on functional outcomes, particularly in well-controlled trials. The failure of Study 301 to meet its primary endpoint, coupled with the exploratory nature of the secondary analyses, falls short of this standard. Overall, the FDA's decision to expand approval for delandistrogene moxeparvovec in DMD patients is not supported by substantial evidence of effectiveness. The failure of the pivotal Study 301 to meet its primary endpoint, coupled with the exploratory nature of secondary analyses and limited data in non-ambulatory patients, does not justify the broad indication granted. This approval sets a concerning precedent that may undermine the FDA's credibility and the integrity of the drug approval process.

Moving forward, it is imperative that the FDA adheres to its established standards for substantial evidence of effectiveness, even in the face of pressure to approve treatments for rare, serious conditions. Additional well-controlled studies may be beneficial to identify potential subgroups of DMD patients for whom delandistrogene moxeparvovec could provide meaningful clinical benefit. Furthermore, the accelerated approval pathway should be reevaluated to ensure that it maintains an appropriate balance between providing early access to promising therapies and upholding rigorous standards of evidence.

While the urgent need for effective DMD treatments is clear, approving therapies without adequate evidence of efficacy does a disservice to patients, healthcare providers, and the broader scientific community. It is important to consider how decisions about drug approvals can be balanced to incorporate both robust scientific evidence and the urgent needs of patients with rare diseases. The case of delandistrogene moxeparvovec serves as a stark reminder of the challenges in balancing scientific rigor with the desire to provide hope for patients with devastating diseases, and it should prompt a thorough reexamination of the FDA's approval processes, particularly for therapies targeting rare diseases.

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ORCID

Larry E Miller http://orcid.org/0000-0003-1594-1885

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