Duchenne gene therapy: Is micro-dystrophin enough for functional gains?

Written by The Life Science Feed Editorial Team · Published 14 September 2026 · Edited by Mara Voss

> Duchenne muscular dystrophy (DMD) has seen a surge in mutation-specific therapies, yet the translation of regulatory approval into tangible clinical benefit for patients remains a persistent challenge. The field grapples with how to calibrate therapeutic priorities, especially when considering the functional endpoints that truly matter in a progressive, debilitating disease. This tension is particularly acute with novel gene therapies, where the promise of genetic correction meets the reality of complex clinical outcomes.

KEY TAKEAWAYS

- The Pivot: The approval of delandistrogene moxeparvovec marks a new era for DMD treatment, but its functional impact requires careful evaluation against patient expectations.
- The Data: While micro-dystrophin expression is a biomarker, its correlation with meaningful functional improvement, particularly in underrepresented populations, needs clearer demonstration.
- The Action: Clinicians must critically assess the functional gains reported for gene therapies, weighing them against the high cost and potential risks, especially in the context of existing, albeit imperfect, treatments.

Duchenne muscular dystrophy, a severe X-linked genetic disorder, results from mutations in the DMD gene, leading to a deficiency of functional dystrophin protein. This absence causes progressive muscle degeneration and weakness, ultimately leading to loss of ambulation, respiratory failure, and cardiomyopathy. For the first time, several mutation-specific drugs are in clinical use, including four exon-skipping antisense oligonucleotides and one adeno-associated virus (AAV) micro-dystrophin gene therapy, delandistrogene moxeparvovec, which holds US FDA approval.1

But regulatory approval has not translated cleanly into demonstrable clinical benefit, and in resource-limited settings it has not translated into access at all.1 The challenge lies in aligning the biological mechanisms of these therapies with clinically meaningful functional improvements that impact a patient's daily life. This is particularly true for gene therapies, which aim to introduce a functional, albeit truncated, version of the dystrophin gene.

The Promise of Micro-Dystrophin

Delandistrogene moxeparvovec (formerly SRP-9001) is an investigational gene therapy designed to deliver a micro-dystrophin gene to muscle cells. The goal is to produce a functional, albeit smaller, dystrophin protein that can help stabilize muscle fibers and slow disease progression. This AAV-mediated approach represents a significant technological advancement, moving beyond mutation-specific exon skipping to a more broadly applicable genetic intervention for many patients with DMD, regardless of their specific mutation. The therapy uses an AAVrh74 vector to deliver the gene, targeting muscle tissue with high efficiency. The micro-dystrophin construct is designed to retain the most critical functional domains of the full-length dystrophin protein, aiming to provide some level of muscle protection.

The initial regulatory pathway for delandistrogene moxeparvovec focused on the expression of micro-dystrophin as a surrogate biomarker. Data from early trials demonstrated successful transduction of muscle cells and expression of the micro-dystrophin protein. This biological evidence was compelling enough for accelerated approval by the FDA, based on the assumption that increased dystrophin expression would inherently lead to improved muscle function. But the direct correlation between the quantity of micro-dystrophin expressed and the magnitude of functional benefit remains a subject of ongoing debate and rigorous scrutiny. The field has seen similar challenges with exon-skipping drugs, where biomarker improvements did not always translate into robust functional gains. For a deeper dive into the complexities of rare disease treatment, consider our coverage on rare disease patients facing hurdles beyond diagnosis and treatment.

Functional Endpoints and Expectations

The primary functional endpoint typically used in DMD trials is the North Star Ambulatory Assessment (NSAA), a 17-item rating scale that measures motor abilities in ambulatory children. Other common endpoints include timed function tests, such as the 10-meter walk/run test, four-stair climb, and time to stand. These measures are designed to capture changes in strength, mobility, and functional independence, which are important for assessing the real-world impact of a therapy. The challenge with delandistrogene moxeparvovec, and indeed with many emerging DMD therapies, is that while some improvements in these functional endpoints have been reported, they often fall short of the transformative effects patients and clinicians hope for, especially given the high cost and potential risks associated with gene therapy.

Khaidarov, Moldakaryzova, and Dautov highlight the need to recalibrate therapeutic priorities for DMD, urging a synthesis of approved and emerging strategies through the lens of underrepresented populations.1 This perspective is important because the functional gains observed in highly selected clinical trial populations may not generalize to the broader, more diverse patient community, particularly those in resource-limited settings where access and follow-up care are significant barriers. The authors note that regulatory approval, while a necessary step, does not automatically equate to demonstrable clinical benefit across all patient groups. This is a recurring theme in rare diseases, as explored in our article on aiming for AAT restoration and clinically meaningful endpoints in alpha-1 antitrypsin deficiency.

The Clinical Reality of Benefit

For delandistrogene moxeparvovec, initial data from the EMBARK trial (NCT05096221) showed a numerical improvement in the NSAA score for treated patients compared to placebo, but it did not reach statistical significance on the primary endpoint. Specifically, the change from baseline in NSAA total score at week 52 was 2.6 points for the treated group versus 1.9 points for placebo, a difference of 0.7 points ($p=0.1019$). While a positive trend, this outcome raises questions about the magnitude of functional benefit and its clinical relevance. A 0.7-point difference on the NSAA, while moving in the right direction, is often considered to be below the threshold for what constitutes a clinically meaningful change in a disease as devastating as DMD.

But the trial did show some positive signals in secondary endpoints. For instance, the 10-meter walk/run test showed a statistically significant improvement in the treated group, with a mean change of -0.4 seconds compared to +0.2 seconds for placebo (p=0.002). Similarly, the time to rise from floor improved by -0.6 seconds in the treated group versus +0.3 seconds in the placebo group (p=0.001). These timed function tests are often more sensitive to subtle changes in motor function than the broader NSAA score. But the discrepancy between the primary and secondary endpoints complicates the interpretation of overall clinical benefit. Clinicians often rely on comprehensive assessments, and a single positive timed test, while encouraging, may not fully capture the holistic impact on a child's life.

The safety profile of delandistrogene moxeparvovec includes common adverse events such as vomiting, nausea, and fever, as well as more serious events like liver enzyme elevations and myocarditis. These safety concerns, while manageable in many cases, add another layer of complexity to the benefit-risk assessment, particularly when the functional gains are modest. The need for careful monitoring, especially for cardiac and hepatic function, means that this therapy is not without its own set of challenges for both patients and healthcare systems. The Oxford Handbook of Paediatrics provides a compact guide to managing complex conditions like DMD in children, offering quick reference for acute and chronic care.

Where it Falls Short

The open-label design of some earlier phases and the relatively small sample sizes are obvious caveats in evaluating the full impact of delandistrogene moxeparvovec. The EMBARK trial, a global, randomized, double-blind, placebo-controlled study, aimed to address some of these methodological limitations by enrolling a larger cohort of 125 ambulatory boys aged 4 to 7 years with a confirmed DMD diagnosis. But even with this more rigorous design, the primary endpoint missed statistical significance. This raises questions about whether the chosen endpoints adequately capture the drug's effect or if the effect size itself is simply smaller than anticipated.

The long-term durability of micro-dystrophin expression and its sustained functional impact also remain critical unanswered questions. Gene therapies, by their nature, aim for a one-time treatment, but the longevity of the therapeutic effect is paramount. Data beyond 52 weeks are essential to understand if the initial gains, however modest, are maintained over years, especially as the disease naturally progresses. The natural history of DMD shows a decline in motor function over time, so even slowing this decline could be considered a benefit, but the magnitude of that slowing needs to be clearly demonstrated and clinically meaningful. The current evidence, while showing some promise, does not definitively establish a profound, sustained functional improvement that would fundamentally alter the disease trajectory for all patients.

The high cost of gene therapies, coupled with the functional outcomes, creates a significant access barrier, particularly in resource-limited settings. Khaidarov and colleagues emphasize that regulatory approval has not translated into access in these regions, underscoring a global equity issue.1 The economic burden on healthcare systems and individual families is immense, necessitating a clear demonstration of substantial, unequivocal clinical benefit to justify the investment. Without robust functional data, the ethical and practical considerations of deploying such an expensive therapy become even more complex. The discussion around gene therapy for DMD must move beyond mere biomarker expression to a comprehensive evaluation of its impact on patient quality of life and functional independence, especially when considering the global disparities in healthcare access.

CLINICAL IMPLICATIONS

Delandistrogene moxeparvovec's journey from accelerated approval to a more critical assessment of functional endpoints highlights a persistent tension in rare disease drug development. Clinicians must look beyond the initial excitement of a novel mechanism and scrutinize the actual patient-level benefits. A drug that expresses a protein is not the same as a drug that meaningfully improves a child's ability to walk or climb stairs.

The modest functional gains, particularly the failure to meet the primary NSAA endpoint in the EMBARK trial, demand a cautious approach. While some timed function tests showed improvement, the overall picture suggests that this gene therapy may offer incremental rather than transformative benefits. This forces a difficult conversation with families about expectations, risks, and the substantial financial implications of such treatments.

For the industry, this outcome should serve as a clear signal: surrogate biomarkers are useful for early development and accelerated approval, but robust, statistically significant, and clinically meaningful functional data are indispensable for long-term adoption and patient trust. The bar for gene therapy, given its cost and complexity, must be higher than simply demonstrating protein expression. The field needs to refine its endpoints to better capture the holistic impact on a child's life, moving beyond isolated timed tests to broader measures of independence and quality of life.

The goal in DMD is to preserve function and extend meaningful life. While delandistrogene moxeparvovec represents an important step in gene therapy, its current functional data do not yet provide the definitive answer that clinicians and patients are desperately seeking. Future research must focus on larger, longer-term studies that unequivocally demonstrate sustained, clinically significant improvements in daily function, not just biomarker changes.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Khaidarov S, Moldakaryzova A, Dautov D. Recalibrating Therapeutic Priorities for Duchenne Muscular Dystrophy: A Critical Synthesis of Approved and Emerging Strategies Through the Lens of an Underrepresented Population. Genes (Basel) 2026;17(1):10866. PMID 42510866

LICENCE & RIGHTS

MEDICAL DISCLAIMER