Delandistrogene Moxeparvovec: Are Functional Endpoints Meeting Duchenne Expectations?

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Duchenne muscular dystrophy (DMD) has seen a surge in mutation-specific therapies, with several now holding regulatory approval. But the journey from regulatory green light to demonstrable, meaningful clinical benefit for patients has been anything but straightforward, particularly when assessing functional endpoints against the high expectations set for these innovative treatments. The critical question for clinicians remains whether these therapies truly alter the disease trajectory in a way that matters to patients and their families.

KEY TAKEAWAYS

- The Pivot: While several mutation-specific drugs for Duchenne muscular dystrophy have gained regulatory approval, their translation into clear, demonstrable clinical benefit remains a challenge.
- The Data: One adeno-associated virus (AAV) micro-dystrophin gene therapy holds US FDA approval, but its functional impact requires careful scrutiny against the backdrop of an underrepresented patient population.
- The Action: Clinicians must critically evaluate the functional endpoints reported for novel DMD therapies, understanding that regulatory approval does not automatically equate to broad, accessible, or clinically transformative patient outcomes.

Duchenne muscular dystrophy, a devastating X-linked genetic disorder, has long presented a formidable challenge to therapeutic development. The disease, characterised by progressive muscle degeneration and weakness due to the absence or dysfunction of dystrophin, leads to severe functional impairment and premature death. For decades, management focused on supportive care, but genetic insights have spurred the development of mutation-specific interventions. These include exon-skipping antisense oligonucleotides, nonsense-readthrough agents, and gene therapies designed to deliver a functional dystrophin gene or a micro-dystrophin analogue. The emergence of these therapies, while a sign of scientific progress, has also introduced a complex market where regulatory success does not always align with the practical realities of clinical efficacy and patient access.1

The current therapeutic arsenal for DMD includes four exon-skipping antisense oligonucleotides and one adeno-associated virus (AAV) micro-dystrophin gene therapy, delandistrogene moxeparvovec, all of which have secured US FDA approval. An additional nonsense-readthrough agent, ataluren, holds a conditional European authorisation, though this approval is currently under review and the drug has never been approved by the FDA. These approvals represent significant milestones, but the clinical community, particularly European GPs and specialists, must scrutinise the functional endpoints that underpinned these decisions, especially for novel gene therapies like delandistrogene moxeparvovec.1

The Promise and the Practicalities of Gene Therapy

Delandistrogene moxeparvovec is an investigational gene therapy designed to deliver a gene that codes for a shortened, but functional, version of dystrophin, known as micro-dystrophin. The rationale is straightforward: by providing a functional protein, the therapy aims to mitigate the progressive muscle damage characteristic of DMD. This approach leverages an AAV vector to deliver the micro-dystrophin gene to muscle cells. The promise of such a therapy is immense, offering the potential to address the root cause of the disease rather than merely managing its symptoms. But the practical translation of this genetic correction into tangible, sustained functional improvement for patients is the ultimate measure of success.1

The regulatory pathway for delandistrogene moxeparvovec involved a careful assessment of its ability to produce micro-dystrophin in muscle tissue and, for patients, to translate this biochemical effect into clinical benefit. The FDA's approval hinged on data demonstrating micro-dystrophin expression, but the functional endpoints, which are paramount for clinicians and patients, have been a subject of ongoing debate. The challenge lies in establishing a clear, dose-dependent relationship between micro-dystrophin levels and improvements in motor function, ambulation, and quality of life. Without robust evidence linking these, the therapy's role in routine clinical practice becomes less clear.1

Functional Endpoints: What Was Measured, What Was Expected

Clinical trials for DMD therapies typically rely on a battery of functional endpoints to assess efficacy. These often include the North Star Ambulatory Assessment (NSAA), a 17-item rating scale that measures motor function in ambulatory children with DMD; timed function tests such as the 10-meter walk/run, 4-stair climb, and stand from supine; and measures of muscle strength. The expectation for a gene therapy like delandistrogene moxeparvovec is that it would significantly improve these measures, or at least slow their decline, compared to natural history or placebo. The magnitude of improvement, and its durability, are critical considerations for clinicians making prescribing decisions.1

One of the persistent challenges in DMD trials is the heterogeneity of the patient population, particularly regarding

age and disease progression. Younger, ambulatory patients often show a different response profile than older, non-ambulatory individuals. This makes direct comparisons across trials and therapies difficult. The initial studies supporting delandistrogene moxeparvovec focused on specific age groups, and the generalisability of these findings to the broader DMD population, especially those in later stages of the disease, remains an open question. Clinicians must consider whether the observed benefits, if any, are truly meaningful for the diverse patients they see in practice.1

The Data: Reading the Lines of Approval

The approval of delandistrogene moxeparvovec by the US FDA marked a significant moment for the DMD community. But the specific data supporting functional improvement requires careful interpretation. The available research, including a critical synthesis by Khaidarov, Moldakaryzova, and Dautov in Genes (Basel), highlights that regulatory approval has not translated cleanly into demonstrable clinical benefit across all approved DMD therapies.1 This observation extends to gene therapies, where the presence of micro-dystrophin does not automatically equate to a transformative functional outcome. The paper points out that while mutation-specific drugs are now in clinical use, the evidence for their broad clinical impact, particularly in underrepresented populations, is still evolving.1

For delandistrogene moxeparvovec, the initial data focused heavily on the biological endpoint of micro-dystrophin expression. While this is a necessary step, it is not sufficient. The critical question for clinicians is whether this expression translates into improvements in functional measures like the NSAA score or timed tests. The clinical trials for this therapy, like many in the rare disease space, often involve relatively small patient numbers, making it challenging to detect statistically significant differences in functional outcomes that are also clinically meaningful. The absence of a clear, large-scale, and long-term functional benefit can leave clinicians in a difficult position when counselling families.1

The context of other approved therapies further complicates the picture. Four exon-skipping antisense oligonucleotides are approved by the FDA, each targeting specific mutations. These therapies, while offering a genetic correction, have also faced scrutiny regarding the magnitude and consistency of their functional benefits. The experience with ataluren, a nonsense-readthrough agent with conditional European authorisation, underscores this point. Despite its approval, its clinical benefit has been placed under review, and it has never gained FDA approval. This pattern suggests that the bar for demonstrating functional efficacy, beyond mere biochemical correction, is rising, and rightly so.1

Where it Falls Short: The Underrepresented and the Unanswered

A significant limitation highlighted by Khaidarov and colleagues is the disparity in access and demonstrable clinical benefit in resource-limited settings and among underrepresented populations.1 This is not merely a logistical issue; it reflects a fundamental gap in the evidence base. If a therapy's benefits are primarily observed in a highly selected, well-resourced patient cohort, its real-world applicability to a broader, more diverse population becomes questionable. The trial designs for delandistrogene moxeparvovec, like many advanced therapies, may not have adequately captured the experiences of these underrepresented groups, leaving clinicians without clear guidance for a substantial portion of their patient base.

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 lasting effect, but the immune response to the AAV vector and the potential for waning expression over time are concerns. Without extensive long-term follow-up data, clinicians cannot confidently predict the trajectory of benefit for patients receiving delandistrogene moxeparvovec. This uncertainty

adds another layer of complexity to treatment decisions, particularly given the high cost and potential risks associated with gene therapy. For a comprehensive understanding of the disease and its management, clinicians might consult resources like the Oxford Handbook of Paediatrics, which provides a compact guide to acute and chronic paediatric conditions.

Another area of concern is the potential for off-target effects and adverse events associated with AAV gene therapy. While generally considered safe, the systemic delivery of viral vectors carries inherent risks, including immune reactions, liver toxicity, and potential integration into the host genome. These safety considerations must be weighed carefully against the observed functional benefits, especially if those benefits are modest or inconsistent. The balance of risk and reward is particularly delicate in a paediatric population with a life-limiting illness. Our previous coverage on why transthyretin amyloid cardiomyopathy remains underdiagnosed also touches upon the complexities of rare disease diagnosis and treatment, a theme that resonates strongly with DMD.

The definition of "clinically meaningful" improvement is also subjective and can vary between regulatory bodies, clinicians, and patients. A statistically significant change in a functional endpoint may not always translate into a noticeable difference in a child's daily life or their family's burden of care. For a therapy like delandistrogene moxeparvovec, the expectation is not just a marginal slowing of decline, but a tangible improvement in mobility, independence, and overall quality of life. The current evidence base, while supporting regulatory approval, has yet to definitively demonstrate this level of transformative impact across the board. The challenges faced by rare disease patients beyond diagnosis and treatment are a constant reminder of the high stakes involved.

The economic implications of these high-cost therapies also cannot be ignored. In resource-limited settings, the availability of such treatments is often severely restricted, regardless of regulatory approval. This creates an ethical dilemma where effective, albeit expensive, therapies are out of reach for many who could potentially benefit. The global disparity in access, as highlighted by Khaidarov and colleagues, means that a significant portion of the DMD population may never receive these treatments, further complicating the assessment of their real-world impact.1 This issue is not unique to DMD, as seen in discussions around AATD therapies aiming for AAT restoration.

While delandistrogene moxeparvovec represents a scientific triumph in gene therapy, the clinical community must maintain a critical perspective on its functional endpoints. The journey from genetic correction to demonstrable, sustained, and accessible clinical benefit is long and fraught with challenges. The current evidence provides a foundation for hope, but it also underscores the need for continued rigorous evaluation, particularly concerning long-term functional outcomes and equitable access for all patients with Duchenne muscular dystrophy. The field needs more than just micro-dystrophin expression; it needs unequivocal evidence of improved lives.

> **CLINICAL IMPLICATIONS**
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> The approval of delandistrogene moxeparvovec for Duchenne muscular dystrophy, while a scientific achievement, places a significant burden on clinicians to interpret its true functional impact. Regulatory nods, particularly in rare diseases, often hinge on surrogate endpoints or early phase data, which do not always translate into the robust, sustained improvements patients and their families desperately need. We must look beyond the initial excitement and demand clear, long-term data on ambulation, strength, and quality of life. For European GPs and specialists, the challenge is compounded by the conditional nature of some approvals

> and the stark reality of access disparities. Ataluren's conditional authorisation and subsequent review serve as a cautionary tale: a drug can be approved, but if the clinical benefit is not consistently demonstrable, its utility is rightly questioned. This means that while gene therapy offers hope, it also demands a higher standard of evidence for functional outcomes, not just biochemical markers.
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> The industry must recognise that the ultimate measure of success for these high-cost therapies is not just regulatory approval, but widespread, equitable access and a clear, clinically meaningful difference in patients' lives. Without addressing the issues of cost, access, and the generalisability of trial data to underrepresented populations, even the most innovative therapies risk becoming symbols of scientific progress rather than instruments of widespread clinical improvement. The focus must shift from merely getting a drug to ensuring it genuinely transforms patient care.

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