

Gene therapy approval for Duchenne muscular dystrophy: a European perspective

Gene therapy has emerged as a promising approach to previously untreatable conditions, including Duchenne muscular dystrophy (DMD), a progressive disorder caused by DMD mutations that leads to early loss of ambulation and premature death. As dystrophin complementary DNA exceeds the capacity of current viral vectors, microdystrophin transgenes have been developed.¹ Microdystrophin gene transfer substantially modifies disease progression in animal models.^{2,3}

The US Food and Drug Administration (FDA) Accelerated Approval Program allows for earlier approval of drugs that treat serious conditions with unmet needs based on a reasonably validated surrogate endpoint that predicts clinical benefit.⁴ In June, 2023, the US FDA granted accelerated approval to the rAAVrh74 microdystrophin gene therapy delandistrogene moxeparvovec (marketed as Elevidys) for ambulatory patients aged 4–5 years with DMD on the basis of transgene expression in a phase 2 trial (NCT03769116) involving patients aged 4–7 years, where the functional endpoint (North Star Ambulatory Assessment [NSAA] score) showed no statistically significant difference.^{5,6} Post-hoc analyses suggested benefit in patients aged 4–5 years, but US FDA statisticians advised caution due to the non-significant overall outcome.⁵ A confirmatory trial was required to show clinical benefit for full approval.

This phase 3 trial (NCT05096221) did not meet statistical significance for its primary endpoint (NSAA score) despite robust transgene expression.⁷ Following a supplemental Biologics License Application for traditional approval in patients older than 4 years with DMD, the US FDA's Offices of

Clinical Evaluation, Therapeutic Products, and Biostatistics and Pharmacovigilance Division of Biostatistics issued a Complete Response recommendation, rejecting the application.^{8,9} In June, 2024, the Center for Biologics Evaluation and Research Director overturned this rejection, citing benefits in secondary outcomes despite US FDA statisticians deeming them uninterpretable.^{9,10} The decision emphasised correlations between secondary outcomes and microdystrophin expression.¹⁰ Delandistrogene moxeparvovec thus received full approval for ambulatory patients older than 4 years, despite unproven efficacy compared with placebo. Similarly, another phase 3 adeno-associated virus (AAV)-based gene therapy trial (NCT04281485) involving a different microdystrophin construct, fordadistrogene movaparvovec, also did not show clinical efficacy, despite high microdystrophin expression (85%) in treated patients versus low microdystrophin expression (6% within the background noise of the measure) in patients receiving placebo.^{11,12}

Both phase 3 trials used the NSAA score as the primary efficacy endpoint; the NSAA is a validated functional measure where a two-point or three-point change is clinically significant.¹³ The uncontrolled phase 1 trial of delandistrogene moxeparvovec in four patients aged 4–7 years reported improvement of up to 8 points.¹⁴ However, disease progression varies widely; some boys gain function until age 6 years or older, whereas others plateau or decline, which complicates assessment of slowed progression from microdystrophin in 48-week trials.^{15,16} In the phase 3 trial, the NSAA least squares mean difference was only 0.65 points ($p=0.2441$) despite substantial transgene expression (34.2% vs 0.0%).⁷ Secondary outcomes numerically favoured treatment over placebo, but did not reach statistical significance due to type 1 error constraints.^{7,9}

Long-term efficacy of delandistrogene moxeparvovec remains unknown. Non-integrating viral vectors such as AAV typically remain as extrachromosomal episomes, which are usually lost during cell division.¹⁷ Caution is needed when extrapolating the promising duration of effect with onasemnogene AAVp (Zincate) in spinal muscular atrophy, in which target neuronal cells are terminally differentiated. In contrast, post-mitotic myofibers have regenerative capacity through stem cells that can enter the cell cycle following injury.¹⁸ Without fully functional microdystrophin, exercise-induced damage and dystrophic processes will continue, and the number of transgenes is expected to decline due to muscle turnover, making long-term transgene expression unpredictable. The immune responses against rAAVrh74 prevent retreatment with delandistrogene moxeparvovec and limit access to other future AAV-based therapies.

Delandistrogene moxeparvovec has manageable short-term side-effects such as nausea, vomiting, and reduced appetite, but also a substantial risk of acute liver injury requiring immunosuppression.⁷ **In March, 2025, a patient died from acute liver failure 2 months post-infusion [A: reference?].** Previous experience with gene therapy in spinal muscular atrophy shows that rare but serious adverse events that might not be observed in clinical trials can emerge with real-world use.¹⁹

Following the US FDA approval, regulatory agencies in Bahrain, Brazil, Israel, Kuwait, Oman, Qatar, and the United Arab Emirates authorised delandistrogene moxeparvovec, prompting access requests from European families and several crowd-funding initiatives. Delandistrogene moxeparvovec is priced at US\$3.2 million. The use of products with uncertain risk-benefit profiles will strain rare-disease budgets, diverting resources from other options and supportive

therapy. The US FDA approval of delandistrogene moxeparvec has thus sparked debate on standards for novel therapies and has far-reaching implications for patients, the DMD community, regulatory standards, and therapy development. Although accelerated approval is crucial for treatments of conditions such as DMD, the benchmark for rare disease therapies must remain high. Efforts should concentrate on understanding the discrepancy between high microdystrophin expression and absent statistically significant functional improvement, whether due to missed therapeutic windows, differences between microdystrophin and full-length dystrophin, or trial design.

Who will benefit from delandistrogene moxeparvec approval in the EU or UK remains uncertain. Given its high cost and single-use nature, more evidence is required to assess its broad impact and justify widespread adoption.

AA-R discloses being a member of the scientific advisory board of Sarepta, the developer of delandistrogene moxeparvec; remuneration for this activity is paid to Leiden University Medical Center. EB has received honoraria for lecture presentations for Biogen and is on the advisory board for Roche, Biogen, Union Chimique Belge, and PTC Therapeutics. LDW has received a research grant from Pfizer; honoraria paid to the KU Leuven for a lecture during a symposium for Dyne Therapeutics and for advisory board roles for Italfarmaco, Roche, Pfizer, Dyne Therapeutics, Santhera Therapeutics, Entrada Therapeutics, Wave Lifesciences, and Genethon; and support from Pfizer for attendance at World Muscle Society 2024 and is secretary of the Belgian Society of Paediatric Neurology. AK has received research grants from Roche, Biogen, and Fondation Suisse de Recherche sur les Maladies Musculaires; has received honoraria paid to her institution for lectures or for advisory board activities for Santhera, Italfarmaco, Roche, Novartis, and Biogen; is vice president of the Swiss paediatric neurology society; and is president of the rare disease network Myosuisse. EN has received a research grant from Pfizer paid to his institution; has received consulting fees paid to his institution from Roche, BioMarin, Italfarmaco, Entrada, Edgewise, Solid, and Avidity; and has received honoraria paid to his institution from Sarepta. LS has received research grants paid to his institution from Roche and Sysnav; has received personal consulting fees from Roche, Sarepta, Pfizer, Solid, PTC Therapeutics, Santhera, Dyne, Wave Life Sciences, Pepgen, Italfarmaco, Sysnav, Biomarin,

Regenexbio, and Myastana; and has participated on a data safety monitoring board for Fibrogen. All other authors declare no competing interests.

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