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 abeparvovec 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.[19] 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.[20]

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

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/

therapy. The US FDA approval of delandistrogene moxeparvovec 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 moxeparvovec 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 moxeparvovec; 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.

*Hannah Jolly, Annemieke Aartsma-Rus, Enrico Bertini, Liesbeth De Waele, Jana Haberlova, Andrea Klein, Erik Niks, *Laurent Servais*
laurent.servais@paediatrics.ox.ac.uk

Department of Paediatrics, MDUK Oxford Neuromuscular Centre & NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford OX3 9DU, UK (HJ, LS); Department of Human Genetics, Leiden University Medical Center, Leiden, Netherlands (AA-R); Research Unit of Neuromuscular and Neurodegenerative Disease, Bambino Gesù Children's Research Hospital, IRCCS, Rome, Italy (EB); Department of Paediatrics, University Hospitals Leuven and Department of Development and Regeneration, KU Leuven, Leuven, Belgium (LDW); Department of Pediatric Neurology, Neuromuscular Reference Centre, University Hospital Motol, Prague, Czech Republic (JH); Division of Neuropaediatrics, Development and Rehabilitation, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (AK); Department of Neurology, Leiden University Medical Center, Leiden, Netherlands (EN); Department of Paediatrics, Neuromuscular Reference Centre, University Hospital of Liège, Liège, Belgium (LS)

1 Duan D. Systemic AAV micro-dystrophin gene therapy for Duchenne muscular dystrophy. *Mol Ther* 2018; **26:** 2337–56.
2 Shin JH, Pan X, Hakim CH, et al. Microdystrophin ameliorates muscular dystrophy in the canine model of Duchenne muscular dystrophy. *Mol Ther* 2013; **21:** 750–57.
3 Le Guiner C, Servais L, Montus M, et al. Long-term microdystrophin gene therapy is effective in a canine model of Duchenne muscular dystrophy. *Nat Commun* 2017; **8:** 16105.
4 US Food and Drug Administration. FDA facts: biomarkers and surrogate endpoints. 2017. https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints (accessed Dec 9, 2024).
5 Adu-Gyamfi E, US Food and Drug Administration. Summary basis for regulatory action. June 21, 2023. https://www.fda.gov/media/169746/download (accessed Jan 27, 2025).
6 Mendell J, Shieh P, Sahenk Z, et al. A phase 2 clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in patients with Duchenne muscular dystrophy (DMD) (S48.004). *Neurology* 2023; **100:** 3035.
7 Mendell JR, Muntoni F, McDonald CM, et al. AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial. *Nat Med* 2025; **31:** 332–41.
8 Fashoyin-Aje LA, Verdun N, US Food and Drug Administration. Office director memorandum: Office of clinical evaluation summary of regulatory decision on biologics license application. 2023. https://www.fda.gov/media/179487/download?attachment (accessed Nov 15, 2024).
9 Zhou T, US Food and Drug Administration. Statistical review supplemental BLA 125781/34. 2024. https://www.fda.gov/media/179489/download?attachment (accessed Nov 15, 2024).
10 Marks P, US Food and Drug Administration. Center Director Decisional Memo BLA 125781/AMENDMENT 34. 2024. https://www.fda.gov/media/179485/download (accessed April 9, 2025).
11 Muntoni F, Nascimento A, Shin J, et al. CIFFREO, a phase 3, randomized, double-blind, placebo-controlled study of fordadistrogene movaparvovec (FM) in ambulatory participants with Duchenne muscular dystrophy (DMD). *Neuromuscul Disord* 2024; **43:** 104459 (abstr 06LBO).
12 Parent Project Muscular Dystrophy. World Muscle Society 2024: CIFFREO data discussion with Pfizer. Oct 18, 2024. https://www.parentprojectmd.org/aiovg_videos/world-muscle-society-2024-ciffreo-data-discussion-with-pfizer/ (accessed Dec 5, 2024).
13 Ayyar Gupta V, Pitchforth JM, Domingos J, et al. Determining minimal clinically important differences in the North Star Ambulatory Assessment (NSAA) for patients with Duchenne muscular dystrophy. *PLoS One* 2023; **18:** e0283669.
14 Mendell JR, Sahenk Z, Lehman K, et al. Assessment of systemic delivery of rAAVrh74.MHCK7.micro-dystrophin in children with Duchenne muscular dystrophy: a nonrandomized controlled trial. *JAMA Neurol* 2020; **77:** 1122–31.
15 Muntoni F, Domingos J, Manzur AY, et al. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. *PLoS One* 2019; **14:** e0221097.
16 Stimpson G, Ridout D, Wolfe A, et al. Quantifying variability in motor function in Duchenne muscular dystrophy: UK centiles for the North Star Ambulatory Assessment, 10m walk run velocity and rise from floor velocity in GC treated boys. *J Neuromuscul Dis* 2024; **11:** 153–66.
17 Smith RH. Adeno-associated virus integration: virus versus vector. *Gene Ther* 2008; **15:** 817–22.
18 Relaix F, Bencze M, Borok MJ, et al. Perspectives on skeletal muscle stem cells. *Nat Commun* 2021; **12:** 692.
19 Sarepta Therapeutics. Community letter: ELEVIDYS safety update. March 18, 2025. https://www.sarepta.com/community-letter-elevidys-safety-update (accessed April 23, 2025).
20 Horton RH, Saade D, Markati T, et al. A systematic review of adeno-associated virus gene therapies in neurology: the need for consistent safety monitoring of a promising treatment. *J Neurol Neurosurg Psychiatry* 2022; **93:** 1276–88.

Revisiting the issue of female genital reinfibulation in HICs

Increased international migration has exposed societies to a diversity of cultural and ethical issues regarding reproductive control in women's