SPECIAL ARTICLE

# Delandistrogene Moxeparvovec Gene Therapy in Individuals With Duchenne Muscular Dystrophy: Evidence in Focus

## Report of the AAN Guidelines Subcommittee

Maryam Oskoui,[1] Tracie Anne Caller,[2] Julie A. Parsons,[3] Laurent Servais,[4] Russell J. Butterfield,[5] Jyoti Bharadwaj,[6] Sean C. Rose,[7] Benjamin Tolchin,[8] Katie Puskala Hamel,[9] Heather M. Silsbee,[9] and James J. Dowling[10]

**Correspondence**
American Academy of Neurology
guidelines@aan.com

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## Abstract

This Evidence in Focus reviews the current evidence on the efficacy and adverse effects of delandistrogene moxeparvovec in patients with Duchenne muscular dystrophy (DMD) and presents clinical considerations regarding use. The author panel systematically reviewed available clinical trial data on delandistrogene moxeparvovec in patients with DMD. The risk of bias was evaluated using the American Academy of Neurology's 2017 therapeutic classification of evidence scheme. Safety information, regulatory decisions, and clinical context were also reviewed. Six clinical trials were identified, of which 4 had peer-reviewed data available. From the 4 studies with available data (2 Class I and 2 Class III), exposure data are available on 134 boys, of which 128 are ambulatory and aged ≥4 to <8 years. Both Class I studies failed to meet the primary functional motor outcome as assessed by change in the North Star Ambulatory Assessment score. Several secondary functional motor outcomes demonstrated improvement in the treatment group with small effect sizes, not meeting statistical significance from hierarchical analysis. Corticosteroid dose exposure was higher in the treatment group in the first 12 weeks after infusion, potentially contributing to measured differences between groups. Safety outcomes were similar across studies with multiple treatment-related adverse events, including peri-infusion effects, immune myositis and myocarditis, thrombocytopenia, and liver toxicity. One death has been reported in an individual who was treated with delandistrogene moxeparvovec outside of a trial. Despite not demonstrating efficacy in its primary outcome, delandistrogene moxeparvovec has been approved by the US Food and Drug Administration (FDA) for use in boys with DMD. This decision was supported by the relative safety of the product and secondary outcome measures data in the phase 3 clinical trial. As the drug may now be actively prescribed in the United States and other countries after FDA approval, providers should be aware of the limitations of the treatment and the need to monitor for immune-related side effects including myocarditis, liver injury, and thrombocytopenia, which may require expanded clinical infrastructure. Additional clinical trials and careful collection of real-world evidence from treated patients will be essential to establish short-term and long-term effectiveness and inform understanding of benefits and risks of delandistrogene moxeparvovec across the lifespan.

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## Introduction

Duchenne muscular dystrophy (DMD) is an X-linked progressive muscle disease caused by pathogenic variants in the *DMD* gene resulting in absence of functional dystrophin protein. Prognosis for affected individuals with DMD has improved with multidisciplinary care and use of corticosteroids, but life expectancy remains reduced.[1,2] Novel disease-modifying therapies

[1]Departments of Pediatrics and Neurology & Neurosurgery, McGill University, Quebec, Canada; [2]Department of Neurology, Cheyenne Regional Medical Center, WY; [3]Department of Child Neurology, Children's Hospital Colorado, Aurora; [4]Department of Pediatrics, University of Oxford, United Kingdom; [5]Department of Pediatric Neurology, University of Utah, Salt Lake City; [6]Muscular Dystrophy Association, Chicago, IL; [7]Nationwide Children's Hospital, and The Ohio State University College of Medicine, Columbus, OH; [8]Department of Neurology, Yale School of Medicine, New Haven, CT; [9]American Academy of Neurology, Minneapolis, MN; and [10]Departments of Neurology and Genetics, University of Pennsylvania, Philadelphia.

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## Glossary

**AAN** = American Academy of Neurology; **AAV** = adeno-associated virus; **ASO** = antisense oligonucleotide therapy; **CBER** = Center for Biologics Evaluation and Research; **CIHR** = Canadian Institutes of Health Research; **COI** = conflicts of interest; **CPK** = creatine phosphokinase; **DMD** = Duchenne muscular dystrophy; **FDA** = Food and Drug Administration; **ICER** = Institute for Clinical and Economic Review; **LSM** = least-squares mean; **LVEF** = left ventricular ejection fraction; **NSAA** = North Star Ambulatory Assessment; **PHS Act** = Public Health Service Act; **rAAVrh74** = recombinant adeno-associated virus rhesus isolate serotype 74; **RMD** = raw mean difference; **TTR** = time to rise.

have reached regulatory approval, including several antisense oligonucleotide therapies (ASOs) targeting restoration of the reading frame by exon skipping. Because the wild-type *DMD* gene, which contains 79 exons and encodes a 14-kb transcript, is larger than the packaging capacity of adeno-associated virus (AAV) vectors (~5 Kb),[3] the gene replacement therapies under development for DMD use truncated constructs of the *DMD* gene ("microdystrophins") containing only the most critical domains. Delandistrogene moxeparvovec (trade name Elevidys) is a single-dose gene transfer therapy developed as a treatment for DMD. It consists of a nonreplicating recombinant adeno-associated virus rhesus isolate serotype 74 (rAAVrh74) vector containing a microdystrophin transgene, producing a truncated microdystrophin protein (138-kDa molecular mass, compared with the 427-kDa size of dystrophin expressed in normal muscle). This first-in-class gene therapy gained initial accelerated approval by the US Food and Drug Administration (FDA) on June 22, 2023, in 4–5-year-old ambulatory boys.[4] There was a subsequent label expansion on June 20, 2024, based on data from the phase 3 clinical trial, granting full approval to use delandistrogene moxeparvovec in ambulatory boys with DMD aged 4 years and older and accelerated approval to use in nonambulatory patients with DMD.

This Evidence in Focus provides a review and summary of the current evidence on the efficacy and adverse effects of delandistrogene moxeparvovec for DMD. This type of systematic review uses an abbreviated version of the American Academy of Neurology (AAN) guideline methodology to highlight the strength of evidence underlying new therapies and facilitate discussion concerning their appropriate use. This process does not generate specific recommendations for care. The accompanying discussion is intended to aid the practicing neurologist, other medical professionals, patients, and families in interpreting the published data to inform clinical decision making.

## Description of the Analytic Process

In May 2024, the AAN Guidelines Subcommittee (eAppendices 1 and 2) initiated development of this Evidence in Focus article and appointed an AAN member with content and methodology expertise (M.O.), AAN Guidelines Subcommittee members (T.C., B.T., and S.C.R.), additional content experts (J.J.D., J.A.P., R.J.B., and L.S.), and a patient advocate (J.B.) to develop this document. Each potential author was required to submit an AAN relationship disclosure form and a copy of their curriculum vitae. The panel leadership, consisting of the lead developer and AAN methodologist (M.O.), AAN staff persons (K.P.H. and K.B.D.), and Guidelines Subcommittee leadership, reviewed the relationship disclosure forms and CVs for financial and intellectual conflicts of interest (COI). These documents were specifically screened to exclude those individuals with a clear financial conflict and those whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended users. As required by the AAN, most (at least 51 percent) of the members (M.O., T.C., J.J.D., S.C.R., B.T., and J.B.) of the development panel and the lead developer (M.O.) are free of COI relevant to the subject matter of this Evidence in Focus. Three of the 9 author panel members were determined to have relevant COI, which were judged to be not significant enough to preclude them from authorship (J.A.P., R.J.B., and L.S.). The developers determined to have COI (J.A.P., R.J.B., and L.S.) were not permitted to review or rate the evidence. These individuals were consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. Conflicted authors also contributed their expertise to the discussion of clinical context. This full author panel was solely responsible for decisions concerning the design, analysis, and reporting of this Evidence in Focus article.

A systematic literature search of PubMed, Cochrane, Clinicaltrials.gov, and the World Health Organization's International Clinical Trials Registry Platform for published articles and clinical trials on treatment of DMD with delandistrogene moxeparvovec was conducted on July 31, 2024, following the search strategy outlined in eAppendix 3. An updated search was performed using the same parameters on October 16, 2024. Because this report focuses on delandistrogene moxeparvovec, studies reporting other DMD gene therapies or disease-modifying therapies were excluded. Data from posted results on clinicaltrials.gov and in available FDA documents were also reviewed. For evidence-based information about adverse reactions, warnings, and precautions, we included all study types of original reports and consulted the FDA drug label. Two panel members independently reviewed titles and abstracts for inclusion. Articles and study data were classified by 2 independent raters following the 2017 AAN therapeutic classification scheme. Class of evidence statements were developed according to the process used for *Neurology* level of

evidence reviews (eAppendix 4). This article was reviewed and approved by the AAN Guidelines Subcommittee and the AAN Quality Committee before submission to *Neurology*.

## Evidence Summary

The initial search yielded 36 articles. Of the reviewed abstracts, 7 were identified as potentially relevant and full-text articles were obtained for review. Each of the 7 articles was reviewed by 2 panel members working independently of each other. The panelists selected 5 articles for inclusion in the analysis reporting on 4 trials. The updated search yielded 23 articles, from which 1 additional article was selected. The list of ongoing trials with or without results was also retrieved from the Clinicaltrials.gov website and FDA documents. The search yielded a total of 6 trials, of which 4 had available data (Figure).

The primary functional motor outcome in these 4 trials is the North Star Ambulatory Assessment (NSAA), a 17-item measure of ambulatory functions with each task graded on a scale of 0 (unable to perform), 1 (able to perform but struggled or needed assistance), or 2 (able to perform independently). The NSAA includes measures of rising from floor, walking, and running, which are also measured in some of the secondary outcomes of the trials, such as time to rise (TTR) and the 10-meter walk/run (10MWR) test. Healthy boys reach a peak of 34 points by the age of 4 years, and boys with DMD typically demonstrate improvements up to the age of 6 years, followed by an average decline of approximately 3.7 points/year after 7 years of age.[5] A minimal clinically important difference of 2.3–3.5 points (depending on the method used for calculation) has been established for the NSAA.[6]

### Efficacy

Table 1 summarizes the 6 clinical trials investigating delandistrogene moxeparvovec, of which 4 had available peer-reviewed published data at the time of this review. Table 2 summarizes the available efficacy data on NSAA scores in ambulatory boys aged ≥4 to <8 years.

The first study (NCT03375164) is a single-site phase 1/2a nonrandomized trial evaluating the safety and tolerability of delandistrogene moxeparvovec, for a duration of up to 5 years after treatment, in 4 ambulatory boys aged ≥4 to <8 years (mean age [SD] = 4.8 [1.0]) with genetically confirmed DMD. The first publication[7] reports the 1-year safety and tolerability of a single dose of $2.0 \times 10^{14}$ vector genomes per kilogram (vg/kg) of rAAVrh74.MHCK7.microdystrophin (delandistrogene moxeparvovec), given through the peripheral IV route. An additional 1 mg/kg of daily prednisone was initiated on the day before infusion and continued for at least 30 days. Exploratory secondary outcomes included both evaluation of biomarkers at 12 weeks and functional motor outcomes at 1 year without a comparator group (Class IV, insufficient evidence for efficacy). A subsequent publication[8] reports long-term safety data in addition to framing the exploratory functional motor outcomes with a post hoc propensity score–weighted external control (Class III). Relative to the external control cohort (N = 21), a 9-point difference in

**Figure** Study Selection Flowchart

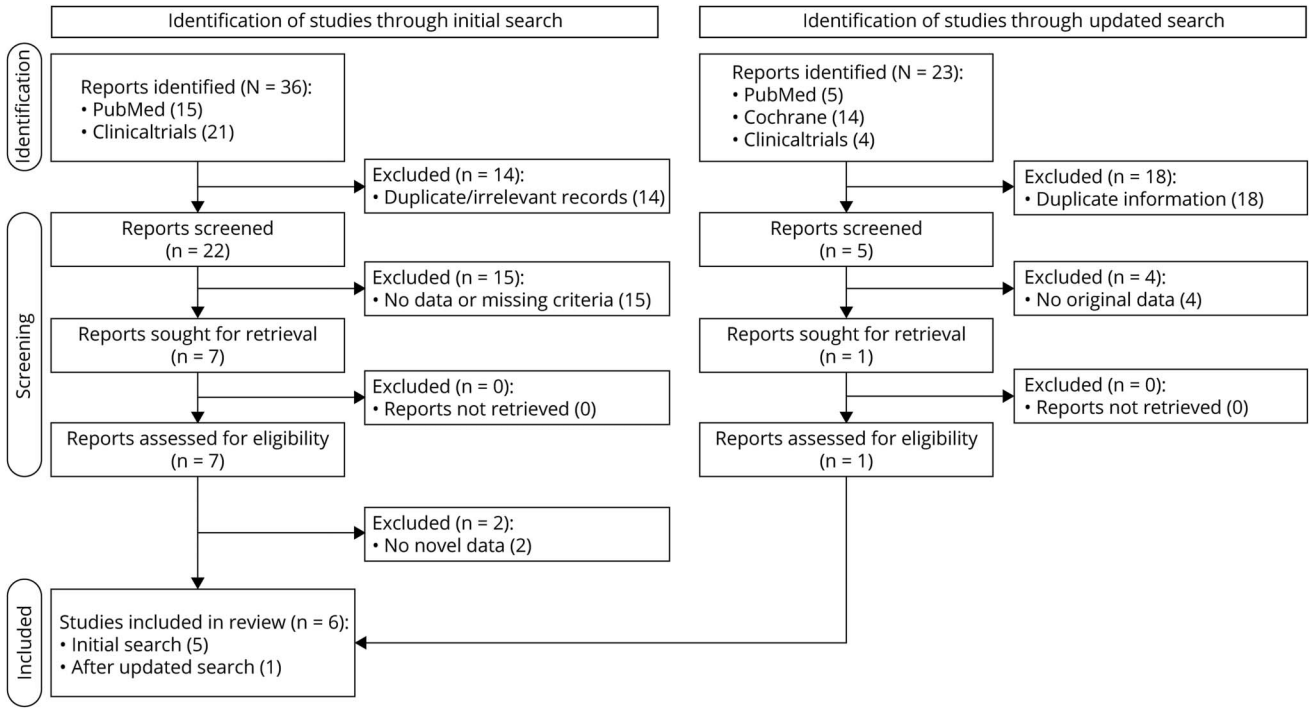

**Table 1** Clinical Trials of Delandistrogene Moxeparvovec in Patients With DMD

| Study name (NCT number) | Study design | Status (study dates)[a] | Number enrolled | Population studied: key inclusion criteria[c] | Delandistrogene moxeparvovec doses studied | Level of evidence (explanation) | Primary outcome |
|---|---|---|---|---|---|---|---|
| **SRP-9001-101 (NCT03375164)** | Open-label, phase 1/2a, single site | Completed (2018-01-04 to 2023-04-25) | 4 | Cohort A: ≥3 mo to <4 y of age, no previous treatment with corticosteroids<br>Cohort B: ambulatory patients, ≥4 to <8 y of age, on stable dose of corticosteroids for at least 12 wk<br>Involving exons 18–58 | $2.0 \times 10^{14}$ vg/kg[b] | Class IV[7] (no comparator group)<br>Class III,[8] 4-y efficacy (external control, baseline differences not shown, important confounder not adjusted for) | Safety |
| **SRP-9001-102 (NCT03769116)** | Randomized, double-blind, placebo-controlled, multicenter, 3-part clinical study, phase 2 | Completed (2018-12-05 to 2023-08-16) | 41<br>4–5-year-old subgroup (8 treated, 8 placebo)<br>6–7-year-old subgroup (12 treated, 13 placebo) | Ambulatory patients, ≥4 to <8 y of age, on stable dose of corticosteroids for at least 12 wk, involving exons 18–58 | Part 1: 8 of 20 received $1.33 \times 10^{14}$ vg/kg, 6 of 20 received $8.94 \times 10^{13}$ vg/kg, and 6 of 20 received $6.29 \times 10^{14}$ vg/kg<br>Part 2: all received $1.33 \times 10^{14}$ vg/kg | Class I for part 1 (results using parallel placebo) and Class III for part 2 (external comparator)[9] | Part 1:<br>Change from baseline in quantity of microdystrophin protein expression as measured by the Western blot at wk 12, AND change from baseline in the total NSAA score at wk 48 |
| **SRP-9001-103 ENDEAVOR (NCT04626674)** | Open-label, phase 1b | Ongoing (start 2020-11-23, estimated completion 2026-07-31) | Cohort 1<br>N = 20<br>Cohort 2<br>N = 7<br>Cohort 3<br>N = 6<br>Cohort 4<br>N = 7<br>Cohort 5a<br>N = 6<br>Cohort 5b<br>N = 2<br>Cohort 6 target<br>N = 6<br>Cohort 7 target<br>N = 4–6 | On stable dose of corticosteroids for at least 12 wk<br>Cohort 1: ambulatory patients, ≥4 to <8 y of age, involving exons 18–79<br>Cohort 2: ambulatory patients, ≥8 to <18 y of age, involving exons 18–79<br>Cohort 3: nonambulatory patients, 9–20 y of age, involving exons 18–79<br>Cohort 4: ambulatory patients, ≥3 to <4 y of age, involving exons 18–79<br>Cohort 5: ≥4 to 9 y of age with pathogenic variants involving exons 1–17 excluding those involving exons 9–13, divided into ambulatory cohort (5a) and nonambulatory cohort (5b)<br>Cohort 6: ambulatory patients, ≥2 to <3 y of age, involving exons 18–79<br>Cohort 7: nonambulatory patients, involving exons 18–79 | $1.33 \times 10^{14}$ vg/kg | 1-y interim cohort 1 results, Class III[10] (external comparator)<br>Information on cohorts 2–5 from "June 18, 2024 Integrated Clinical and Clinical Pharmacology Review Memo—ELEVIDYS," retrieved from fda.gov/vaccines-blood-biologics/tissue-tissue-products/elevidys | Part 1: change from baseline in quantity of SRP-9001 microdystrophin protein expression as measured by the Western blot at wk 12 |
| **SRP-9001-301 EMBARK (NCT05096221)** | Phase 3, multinational, 2-part randomized, double-blinded, placebo-controlled trial | Fully enrolled (start 2021-10-27, estimated completion 2024-11-30) | N = 125<br>63 treated, 62 placebo | Ambulatory patients, ≥4 to <8 y of age, on stable dose of corticosteroids for at least 12 wk<br>Involving exons 18–79 | $1.33 \times 10^{14}$ vg/kg | Class I[11] (for part 1 results using parallel placebo) | Change from baseline in the total NSAA score at wk 52 |

Continued

**Table 1** Clinical Trials of Delandistrogene Moxeparvovec in Patients With DMD *(continued)*

| Study name (NCT number) | Study design | Status (study dates)[a] | Number enrolled | Population studied: key inclusion criteria[c] | Delandistrogene moxeparvovec doses studied | Level of evidence (explanation) | Primary outcome |
|---|---|---|---|---|---|---|---|
| **SRP-9001-302 ENVOL (NCT06128564)** | Open-label, phase 2 | Ongoing (start 2023-11-29, estimated completion 2032-11-30) | N = 21 | Steroid-naive, ambulatory patients, involving exons 18–79, <4 y of age<br>Cohort A: ≥3 to <4 y of age<br>Cohort B: ≥2 to <3 y of age<br>Cohort C: >6 mo to <2 y of age<br>Cohort D: ≤6 mo of age | $1.33 \times 10^{14}$ vg/kg | NA | Safety |
| **SRP-9001-303 ENVISION (NCT05881408)** | Phase 3, multinational, randomized, double-blind, placebo-controlled trial | Ongoing (start 2023-05-31, estimated completion 2027-01-31) | 148 (120 nonambulatory) | ≥8 to <18 y of age, on stable dose of corticosteroids for at least 12 wk, involving exons 18–79<br>Cohort 1: nonambulatory Cohort 2: ambulatory | $1.33 \times 10^{14}$ vg/kg | NA | Part 1: Change from baseline in the total score of PUL assessment (version 2.0) at week 72 |

Abbreviations: NA = not applicable; NSAA = North Star Ambulatory Assessment; PUL = performance of upper limb; SRP-9001 = delandistrogene moxeparvovec.
Note: studies SRP-9001-101 and SRP-9001-102 used a manufacturing process at Nationwide Children's Hospital while a subsequent commercial process was used in all subsequent studies.
[a] As indicated in clinicaltrials.gov as of November 11, 2024.
[b] Estimated by supercoiled standard qPCR, which was subsequently found to be equivalent to a $1.33 \times 10^{14}$ vg/kg dose by linear standard qPCR used in subsequent studies.
[c] All required AANrh74 antibody titers <1:400.

**Table 2** Efficacy Data on NSAA Scores in Ambulatory Boys Aged ≥4 to <8 Years

| Study | NCT number | Phase | N SRP-9001 | N control | Control group | ROB | Time Point | NSAA LSM difference | DMD genotypes included |
|---|---|---|---|---|---|---|---|---|---|
| **101 cohort B** | NCT03375164 | Open label phase 1/2a | 4 | 21 | External | Class III | @4 y | 9.4 points, 95% CI 2.02–16.78, $p = 0.0125$ | 18–58 |
| **102 part 1** | NCT03769116 | RCT phase 2 | 20 | 21 | Placebo | Class I (primary)[a] | @48 wk | 0.8 points, 95% CI −0.95 to 2.55, $p = 0.37$ | 18–58 |
| **102 part 1** | NCT03769116 | RCT phase 2 | 19 | 51 | External | Class III | @96 wk | 2.0 points, 95% CI −0.50 to 4.50, $p = 0.1163$ | 18–58 |
| **102 part 2** | NCT03769116 | RCT phase 2 | 21 | 103 | External | Class III | @48 wk | 2.0 points, 95% CI 0.82–3.18, $p = 0.0009$ | 18–58 |
| **103 cohort 1** | NCT04626674 | Open label phase 1b | 20 | 91 | External | Class III | @1 y | 3.2 points, 95% CI 1.59–4.81, $p < 0.0001$ | 18–79 |
| **301 part 1** | NCT05096221 | RCT phase 3 | 63 | 62 | Placebo | Class I (primary)[a] | @52 wk | 0.65 points, 95% CI −0.45 to 1.75, $p = 0.2441$ | 18–44, 46–79 |

Abbreviations: DMD = Duchenne muscular dystrophy; LSM = least-squares mean; NCT = national clinical trial; NSAA = North Star Ambulatory Assessment; RCT = randomized controlled trial; ROB = risk of bias.
[a] Pooling of 2 Class I outcomes shows a difference in NSAA scores at 48–52 wk between delandistrogene moxeparvovec treatment and placebo of 0.69, with 95% CI -0.24 to 1.62, $I^2 = 20$.

mean change from baseline to year 4 of the NSAA score in the 4 treated patients was shown (least-squares mean [LSM] difference 9.4 points, 95% CI 2.02–16.78, single Class III study, insufficient evidence for efficacy).

The second study (NCT03769116) is a 2-site, phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy of delandistrogene moxeparvovec over 2 parts (48 weeks each) in 41 ambulatory boys aged ≥4 to <8 years with a pathogenic *DMD* variant contained between exons 18 and 58 (inclusive).[9] This latter criterion was added after the study was initiated to reduce the risk of immune-mediated myositis. Patients were either randomized to placebo (up to 10 mL/kg of lactated Ringer solution) in part 1 and then treated with delandistrogene moxeparvovec in part 2 or treated with delandistrogene moxeparvovec in part 1 and then treated with placebo in part 2. The day before infusion, the background dose of steroid was increased to ≥1 mg/kg of a glucocorticoid (prednisone equivalent) daily and continued for ≥60 days after infusion in both groups.

The primary analysis of part 1 is based on a 48-week difference in outcome between treatment and placebo groups (Class I), and the analyses of part 1 at 2 years and part 2 at 48 weeks are based on comparisons with an external propensity score–matched control (Class III). The first co-primary outcome in part 1, a change from baseline in delandistrogene moxeparvovec microdystrophin expression at week 12 measured by the Western blot, was achieved (23.82% of the normal level of full-length dystrophin). The second co-primary outcome, a LSM difference in change from the baseline NSAA score at 48 weeks, was not met (LSM difference 0.8 points, 95% CI −0.95 to 2.55, Class I). Among these, in the 4–5-year-old subgroup, there was an LSM difference of 2.5 points (95% CI 0.44–4.56), whereas the LSM difference in the 6–7-year-old subgroup was −0.7 points (95% CI −2.93 to 1.53). The authors highlight that the randomization stratified by age resulted in unbalanced distribution of baseline functional motor scores favoring the placebo group, with more balanced distribution seen in the 4–5-year-old subgroup. For 19 participants treated in part 1, longitudinal outcome to 96 weeks is available in part 2 and compared with an external propensity score–matched group (N = 51). The LSM difference in the NSAA score at 96 weeks was 2.0 points (95% CI −0.50 to 4.50, Class III). For patients treated with delandistrogene moxeparvovec in part 2 (N = 20), there was a between-group LSM difference in the NSAA score after 48 weeks compared with a propensity score–matched external cohort (N = 103) of 2.0 points (95% CI 0.82–3.18, Class III).

Studies NCT03375164 and NCT03769116 described above used a manufacturing process at Nationwide Children's Hospital while a commercial process was used to manufacture delandistrogene moxeparvovec in all subsequent studies. ENDEAVOR (NCT04626674) is an open-label two-part phase 1b trial of delandistrogene moxeparvovec with target enrollment of 58 patients across 7 cohorts over 260 weeks. Cohort 1 of this

study, comprising 20 ambulatory boys aged ≥4 to <8 years with pathogenic *DMD* variants between exons 18 and 79 (inclusive), has published interim data, which were available for review.[10] One day before gene transfer (single IV dose of $1.33 \times 10^{14}$ vg/kg delandistrogene moxeparvovec), an additional 1 mg/kg of glucocorticoid (prednisone equivalent) daily was started and continued for ≥60 days after infusion. The primary outcome of part 1 is the change in delandistrogene moxeparvovec microdystrophin from baseline to week 12 on the Western blot. The exploratory secondary functional motor outcome at 1 year was compared with a propensity score–matched external comparator group (N = 91), with an LSM difference in the change from baseline of 3.2 points (95% CI 1.59–4.81) in NSAA scores between groups (Class III). Using the same external comparator group, treated patients were also faster on the supine-to-stand task at 1 year (LSM difference −1.2 seconds, 95% CI −1.81 to −0.60, Class III) and on the 10MWR test (LSM difference −1.0 seconds, 95% CI −1.63 to −0.37, Class III). The FDA documents refer to non–peer-reviewed information on cohorts 2–5. In the 6 nonambulatory patients in cohort 3 (mean age 15.26 years, SD 4.22), exploratory efficacy on the performance of upper limb assessment is reported to show a change from baseline of −1.5 points (SD 0.8) at 52 weeks and −3.8 points (SD 2.7) at 104 weeks, compared with natural history data showing a change of −6.3 points.[4]

EMBARK (NCT05096221) is a multinational phase 3, randomized, double-blinded, placebo-controlled trial in 126 ambulatory patients aged ≥4 to <8 years with pathogenic variants in *DMD* between exons 18–44 and 46–79 (inclusive).[11] Randomization was stratified by age and NSAA score at baseline. The corticosteroid dose exposure was comparable between groups at baseline and in the first 2 weeks after treatment (raw mean difference [RMD] daily dose 0.01 mg/kg, 95% CI −0.4 to 0.06). However, there was a higher corticosteroid dose exposure in the treated group from week 2 to day 60 (RMD 0.22 mg/kg daily dose, 95% CI 0.05–0.38), as well as from day 60 to week 12 (RMD 0.28 mg/kg, 95% CI 0.05–0.51), returning to comparable levels after week 12. Higher corticosteroid dose exposure can affect functional outcomes measured months after this exposure. The primary outcome of part 1, a difference in change from the baseline total NSAA score at 52 weeks between groups, was not met (LSM difference of 0.65 points; 95% CI −0.45 to 1.75, Class I). There was also no difference between groups in the prespecified age subgroups and baseline NSAA score subgroups. For secondary prespecified hierarchical outcomes reported, no statistical significance can be drawn, although some showed small numeric differences favoring treatment. There was an LSM difference of −0.64 seconds (95% CI −1.06 to −0.23) in TTR and an LSM difference of −0.42 seconds (95% CI −0.71 to −0.13) in the 10MWR, favoring the delandistrogene moxeparvovec–treated group; these findings were also consistent in the age subgroups. The 95th percentile stride velocity, as measured by continuous wear of a Syde device on the ankle, showed an LSM difference of 0.1m/second (95% CI 0.00–0.19) favoring the treated group. The time to ascend 4 steps showed an LSM difference of −0.36 s (95% CI −0.71 to −0.01), and the 100-meter walk/run (100MWR) test showed no difference between groups (LSM −3.29, 95% CI −8.28 to 1.70). The Patient-Reported Outcomes Measurement Information System Mobility (LSM 0.05, 95% CI −0.08 to 0.19) and Upper Extremity (LSM −0.04, 95% CI −0.24 to 0.17) also showed no difference between groups. Of note, vomiting, a common treatment-related adverse reaction, occurred in 54% of treated boys and 0% of boys in the placebo group, potentially unblinding patients and study personnel.

### Safety

A safety data set derived from the trial experiences of 85 patients from studies NCT03375164, NCT03769116, and NCT04626674 identified 13 treatment-related adverse events that required medical intervention, including vomiting, myocarditis, acute liver injury, and immune-mediated myositis.[12] To reduce the risk associated with an immune response, corticosteroids are administered starting 1 day before infusion and continued for at least 60 days. For patients already on a stable daily or intermittent dose of corticosteroids, a 1-mg/kg/day prednisolone equivalent dose is added up to a maximum of 60 mg per day, and for patients not on baseline corticosteroids, a 1.5-mg/kg/day dose is started 1 week before infusion. Delandistrogene moxeparvovec, like other intravenously administered AAV-based gene therapies, is associated with peri-infusion events as well as both innate and adaptive immune responses, mostly occurring within 90 days after infusion. Adverse reactions recorded with an incidence of ≥5% in trials were vomiting, nausea, liver injury, fever, and thrombocytopenia. Elevations in liver transaminases up to 4-fold the normal upper limit were commonly observed, peaking at 60 days and then returning to normal levels with continued corticosteroid use. More serious issues were noted less frequently. Acute serious liver injury has been observed within 8 weeks after administration. Acute serious myocarditis was also observed; patients with reduced left ventricular ejection fraction (LVEF) may be at a higher risk, and trials have excluded patients with LVEF < 40. No cases of thrombotic microangiopathy or cardiogenic shock were observed with delandistrogene moxeparvovec in these studies. One death due to acute liver failure has been reported in an individual who was treated with delandistrogene moxeparvovec outside of a trial.[13] Immune-mediated myositis leading to severe weakness, muscle pain, dysphagia, and/or dyspnea was observed approximately 4 weeks after infusion in some treated patients with deletions in the *DMD* gene that included exons 8 or 9. Insufficient data are available regarding an immune-mediated myositis reaction for patients with deletions in exons 1–17 who may be at risk as well because they were excluded from the pivotal studies of delandistrogene moxeparvovec.

## Regulatory Decisions

The FDA provided an accelerated approval on June 22, 2023, for use in 4–5-year-old ambulant patients. There was

disagreement between members of the review committee regarding whether the application met the regulatory threshold for approval. The Clinical, Clinical Pharmacology, and Statistics review teams and supervisors had concluded that there was insufficient evidence to support the use of expression of microdystrophin as a surrogate end point that is reasonably likely to predict clinical benefit for accelerated approval and recommended complete response.[14] The Review Committee's decision was overridden by the Center for Biologics Evaluation and Research (CBER) director based on the subgroup of participants in study NCT03769116 who showed improvement in the NSAA score at 1 year compared with placebo.[15] On June 20, 2024, the FDA granted full approval for ambulatory patients aged 4 years and older and accelerated approval for nonambulatory patients aged 4 years and older based on additional data received from the sponsor for study NCT05096221 (EMBARK) and study NCT04626674 (ENDEAVOR). This decision was also taken by the CBER director[4] by overriding the complete response recommendation from the Office of Clinical Evaluation, the Office of Therapeutic Products, and the Office of Biostatistics and Pharmacovigilance, Division of Biostatistics.[16] In his decision, he states, "the data and information also provide substantial evidence of effectiveness as described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to support traditional approval under section 351(a) of the Public Health Service Act (PHS Act), in ambulatory individuals 4 years of age and older with a confirmed mutation in the *DMD* gene except in those with any deletion in exon 8 and/or exon 9 in the *DMD* gene, in whom its use is contraindicated. In addition, the Applicant has provided substantial evidence of effectiveness of ELEVIDYS (trade name for delandistrogene moxeparvovec) in non-ambulatory individuals 4 years of age and older, by demonstrating the drug's ability to elevate microdystrophin levels, which is reasonably likely to predict clinical benefit in this population and supports accelerated approval for this population under section 351(a) of the PHS Act pursuant to section 506(c) of the FD&C Act and 21 C.F.R. 601.41."[4] Clinical efficacy remains to be demonstrated in nonambulatory boys, with several studies underway to address this.

The recommended dose of delandistrogene moxeparvovec is $1.33 \times 10^{14}$ vg/kg of body weight (or 10 mL/kg body weight) for patients weighing less than 70 kg or $9.31 \times 10^{15}$ vg total fixed dose for patients weighing ≥70 kg.

# Clinical Context

Based on biological plausibility and on the existing clinical trial data, AAV-microdystrophin gene therapies are not curative. The FDA's broad approval of the first-in-class delandistrogene moxeparvovec for DMD is met with both hope and uncertainty by the medical and patient communities.

## Populations for Use

Delandistrogene moxeparvovec has been approved in individuals with a clinical and genetic diagnosis of DMD, excluding deletions that encompass exons 8–9, aged 4 years and older, regardless of motor function. Currently, exposure data are available on 134 boys who are mostly ambulatory and aged ≥4 to <8 years. Only 6 patients are aged 9–20 years in cohort 3 of study NCT04626674 and nonambulatory, with limited outcome data available in FDA documents. Of the 134 boys exposed with available data, 45 involve exons 18–58, 89 involve exons 18–79, and 63 involve exons 18–44 and 46–79. Ongoing clinical trials (NCT04626674) will contribute additional data on boys with mutations spanning exons 1–8 and 14–17 (N = 8, open label), as well as more data on use in nonambulatory boys (N = 128). The clinical trial program will eventually have treatment exposure data on approximately 304 boys with DMD.

The use of delandistrogene moxeparvovec has not been studied in patients with moderate-to-severe cardiomyopathy (excluding those with LVEF <40%, although the lowest LVEF in trial was 48%), those with severe pulmonary disease, or those with significant neurodevelopmental impairment. Interviews of individuals with DMD or their caregivers have highlighted a tolerance of risk when there is a lack of other available disease-modifying therapies, advocating for a patient-centered risk-benefit assessment.[17] Functional motor outcomes, quality of life, pulmonary function, and cardiac function are the key outcomes highlighted of value to patients and their families, including maintenance of stability across these outcomes.[18,19]

## Measuring Improvement in Motor Function

The phase 3 trial NCT05096221 (EMBARK) of delandistrogene moxeparvovec failed to demonstrate a statistically and clinically important difference between groups on the primary end point of motor improvement on the NSAA. Small numerical improvements in several secondary motor outcomes did not meet statistical significance from their hierarchical analysis plan. Some of these functional motor outcomes, such as the TTR and 10MWR test, overlap with elements of the NSAA, highlighting potential limitations of the NSAA in capturing smaller differences between groups as an ordinal scale. To reduce the chance of random errors caused by multiple comparisons, secondary outcomes need specific statistical considerations.

Measuring the clinical benefit in treated patients and understanding how it is statistically and clinically different from placebo-treated patients having received a similar dose of glucocorticoid is key. The corticosteroid dose and duration exposure while receiving delandistrogene moxeparvovec represents an important confounding variable when interpreting the efficacy data. Administration of gene therapy requires co-administration of higher dose corticosteroids to

lower the immune system response.[20,21] Corticosteroids have been shown to improve strength, timed motor function, and pulmonary and cardiac function; delay progression of scoliosis; and improve survival in DMD.[1] From the available evidence, studies using an external control group did not account for differences in dose and duration exposure to this important confounder.

## Biomarkers of Efficacy

The primary biomarker investigated in the development of delandistrogene moxeparvovec was microdystrophin levels. Microdystrophin levels were calculated by the Western blot on protein extracts from muscle biopsies taken before treatment and 12 weeks after treatment (parts 1 and 2 of the phase 2 trial, SRP9001-102, NCT03769116). They were normalized and then compared with the amount of full-length dystrophin measured in biopsies from healthy male controls. Using this approach, levels of 23.82% vs 0.14% in the placebo group (part 1) and 39.8% (part 2) were achieved. These values were significant compared with baseline (where no microdystrophin was observed, as expected) and in the range where clinical benefit was inferred. It is this latter inference that formed part of the basis of the original accelerated approval granted to delandistrogene moxeparvovec. Of note, microdystrophin levels were further measured in patients from part 1 at 60 months after dosing and an average level of 19.10% was identified compared with baseline expression.[9]

The assertion that meaningful levels of microdystrophin confer clinical benefit is supported by preclinical data, by the anticipated functional replacement associated with the rationally designed miniaturized dystrophin, and by patient data (where large in-frame deletions that retain the domains found in microdystrophin are associated with mild clinical phenotypes).[22] Similar assumptions motivated the accelerated approvals of other dystrophin-modulating therapies (i.e., exon-skipping ASOs), and overall microdystrophin levels fulfill the FDA criteria for biomarker-based accelerated approval.

Assessment of microdystrophin levels is not accessible outside a clinical trial context and is not expected to have a role in the clinical use of delandistrogene moxeparvovec. There are important caveats in the interpretation of the existing microdystrophin data. It is not known whether levels of microdystrophin correlate with levels of full-length "normal" dystrophin on a 1:1 basis. Therefore, the clinical significance of the amount of microdystrophin seen in patient biopsies is unclear. Second, the FDA-accelerated approval was based on the assumption that microdystrophin levels correlate with clinical benefit. In the phase 2 trial, this was supported by the finding of change in NSAA scores in treated 4–5-year-olds. However, in the larger placebo-controlled study (EMBARK), there was no difference in NSAA scores at 1 year between groups. Therefore, it is not clear how to interpret the correlation with microdystrophin seen in the phase 2 trial.

Of note, the phase 3 trial reports on a second biomarker, serum creatine phosphokinase (CPK) levels. Serum CPK is elevated in all ambulant patients with DMD and is known to be extremely variable, both between patients and within patients, based on activity, time of day, age, corticosteroid exposure, and other factors. Although CPK levels on aggregate were lower in treated patients compared with baseline, this in isolation needs to be interpreted with caution as support of therapeutic effect. CPK levels are not anticipated to have utility in the evaluation and monitoring of patients who receive delandistrogene moxeparvovec.[23]

## Safety Monitoring and Infrastructure for Use

Preparation and foresight are necessary to safely deliver gene transfer products, including substantial investment in human and physical infrastructure. Before dosing, the location where the agent will be infused should be identified. Genetic diagnosis must be confirmed, as patients with any deletion of exons 8 and 9 are excluded from treatment. Patients should have antibody testing (to exclude existing immunity against AAV) performed before delivering the agent, with antibodies to rAAVrh74 being ≤1:400 before treatment. Acquisition of the agent and delivery to the dosing location may take several weeks after previous authorization is obtained. Arrangements must be made with the pharmacy to receive, store, and schedule adequate time to prepare the agent on the day of dosing before scheduling the patient for dosing.

Acute hypersensitivity infusion reaction and anaphylaxis during or up to several hours after administration of delandistrogene moxeparvovec have been reported as a rare side effect in clinical trials. Therefore, close monitoring of patients during and for several hours after the infusion is necessary.

Because of the serious adverse events that have been noted in delandistrogene moxeparvovec clinical trials,[12] ensuring close clinical and laboratory monitoring after dosing is an essential part of treatment. Vigilance and urgent reporting of any new or suspected events that may emerge as a wider, more heterogeneous population of patients are treated with this novel therapy are also highly encouraged.

## Coverage Considerations

Each infusion carries a drug cost of $3.2 million, not including other costs related to the infusion in hospital and the close follow-up required.[24] Insurance coverage in the United States will likely vary, with some covering it for all patients with DMD older than 4 years and others considering the treatment investigational or experimental for all indications because of insufficient evidence of a clinical benefit, or instead approving it as medically necessary only for boys who would have met inclusion criteria for the pivotal trials.[25,26] While an Institute for Clinical and Economic Review (ICER) review is not yet available, ICER Chief Medical Officer David Rind has stated: "This is an enormous price tag for a therapy that has failed to meet its primary end point in the 2 randomized trials in which it has been studied and that is clearly not curative."[27]

## Suggestions for Future Research

Several questions remain unanswered about the efficacy and safety of delandistrogene moxeparvovec as an adjunct therapy given in combination with steroids. While changes in secondary outcome measures and increase in microdystrophin levels in treated patient muscle provide some evidence for efficacy, the primary outcome measure was not met in the phase 3 pivotal trial. Robust efficacy of delandistrogene moxeparvovec over placebo remains to be rigorously established. FDA approval was granted for patients beyond the clinical trial parameters, and the safety and efficacy in patients who fall outside these parameters are unknown. It is critical to pursue, collect, and analyze these data so the community can better understand the effectiveness, safety, and limitations of this treatment.

There are additional unanswered questions that will form the basis for future investigation and study. It is not certain how long gene therapy will persist in the body and what will happen to any benefits achieved during the period when the treatment was active. It is anticipated that therapy may not promote expression for an individual's entire lifespan, and thus, issues related to redosing will be important to consider.[28] At present, all patients exposed to gene therapy develop anti-AAV antibodies, and some develop an immune response to the transgene. These expected immune consequences pose a significant challenge for future redosing and for consideration of receiving future viral-based therapies, including those not yet developed. It is also important to consider the potential for late-emerging adverse effects.

The ideal timing of treatment remains to be determined in DMD. Dosing at a younger age, when the muscle has been less affected by disease, could be explored. However, demonstrating short-term efficacy for very young individuals with DMD will pose a challenge, hence a need for consideration of new outcome measures. To achieve dosing of younger individuals, there would need to be renewed efforts at reducing the age at diagnosis and potentially a shift to broad-based screening to detect patients at a sufficiently young age. Newborn screening is feasible for DMD, and some states have added DMD to their newborn screening platforms.

Finally, there are important future considerations for DMD clinical trials. Learning from the delandistrogene moxeparvovec clinical trials, selecting age-appropriate, reproducible, reliable, and meaningful outcome measures is critical. The potential limitations of using the NSAA as a primary outcome measure will need to be carefully weighed. The potential utility of wearable-based data, which offers the advantage of generating a large amount of quantifiable information reflecting the child's usual movements, has gathered regulatory qualification by the European Medical Agency.[29,30] The number of DMD trials using wearables is growing (NCT06138639, NCT04906460, NCT05524883, and NCT06128564). Additional clinical trials and careful collection of real-world evidence from patients treated in the clinical context will be essential to establish short-term and long-term effectiveness and inform understanding of benefits and risk of delandistrogene moxeparvovec across the lifespan.

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## Author Contributions

M. Oskoui: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. T.A. Caller: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.A. Parsons: drafting/revision of the manuscript for content, including medical writing for content. L. Servais: drafting/revision of the manuscript for content, including medical writing for content. R.J. Butterfield: drafting/revision of the manuscript for content, including medical writing for content. J. Bharadwaj: drafting/revision of the manuscript for content, including medical writing for content. S.C. Rose: drafting/revision of the manuscript for content, including medical writing for content. B. Tolchin: drafting/revision of the manuscript for content, including medical writing for content. K. Puskala Hamel: major role in the acquisition of data; study concept or design. H.M. Silsbee: drafting/revision of the manuscript for content, including medical writing for content. J.J. Dowling: drafting/revision of the manuscript for content, including medical writing for content.


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