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CLINICAL RESEARCH SHORT REPORT

See Editorial on pages 4–6 in this issue.

# Long-term safety and functional outcomes of delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy: A phase 1/2a nonrandomized trial

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## Abstract

**Introduction/Aims:** Delandistrogene moxeparvovec is indicated in the United States for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. Long-term delandistrogene moxeparvovec microdystrophin protein (a shortened dystrophin that retains key functional domains of the wild-type protein) expression may positively alter disease progression in patients with DMD. We evaluated long-term safety and functional outcomes of delandistrogene moxeparvovec in patients with DMD.

**Methods:** An open-label, phase 1/2a, nonrandomized controlled trial (Study 101; NCT03375164) enrolled ambulatory males, ≥4 to <8 years old, with DMD. Patients received a single intravenous infusion ($2.0 \times 10^{14}$ vg/kg by supercoiled quantitative polymerase chain reaction) of delandistrogene moxeparvovec and prednisone (1 mg/kg/day) 1 day before to 30 days after treatment. The primary endpoint was safety. Functional outcomes were change from baseline in North Star Ambulatory Assessment (NSAA) and timed function tests.

**Results:** Four patients (mean age, 5.1 years) were enrolled. There were 18 treatment-related adverse events; all occurred within 70 days posttreatment and resolved. Mean NSAA total score increased from 20.5 to 27.5, baseline to year 4, with a mean (standard deviation) change of +7.0 (2.9). Post hoc analysis demonstrated a statistically significant and clinically meaningful 9-point difference in NSAA score, relative

**Abbreviations:** AE, adverse event; DMD, Duchenne muscular dystrophy; EC, external control; FOR-DMD, Finding the Optimum Regimen for DMD; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus serotype rh74; SD, standard deviation; TRAE, treatment-related adverse event.

to a propensity-score–weighted external control cohort (least-squares mean [standard error] = 9.4 [3.4]; $P = .0125$).

**Discussion:** Gene transfer therapy with delandistrogene moxeparvovec treatment is well tolerated, with a favorable safety profile. Functional improvements are sustained through 4 years, suggesting delandistrogene moxeparvovec may positively alter disease progression.

**KEYWORDS**
delandistrogene moxeparvovec, Duchenne muscular dystrophy, dystrophin, gene therapy, microdystrophin, rAAVrh74

## 1 | INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked disease characterized by an absence or near absence of functional dystrophin protein.[1] Supportive ventilation and glucocorticoids can delay loss of functional milestones and increase lifespan by several years; however, DMD remains associated with early mortality, often before 30 years of age.[2] Furthermore, long-term corticosteroid use is associated with numerous side effects.[1,3] Exon-skipping therapies can slow clinical decline,[4] but not all patients with DMD have mutations that are amenable to these treatments. Improved therapeutic options—with fewer adverse effects, greater efficacy, and broader applicability—are needed.

Delandistrogene moxeparvovec, a gene transfer therapy, is currently indicated in the United States for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.[5] It was developed to address the root cause of DMD and uses a recombinant adeno-associated virus serotype rh74 (rAAVrh74) vector for delivery and targeted production of delandistrogene moxeparvovec microdystrophin protein that retains key functional domains in skeletal and heart muscles.[6,7] This vector demonstrates an acceptable safety profile and was chosen due to the low number of patients with pre-existing binding antibody levels within the established eligibility threshold.[6] Safety and functional outcomes after a single intravenous delandistrogene moxeparvovec administration in patients (aged ≥4 to <8 years) were evaluated in an open-label, phase 1/2a, nonrandomized trial (NCT03375164).[6] Treatment was well-tolerated and associated with a robust expression of delandistrogene moxeparvovec microdystrophin protein at the correct sarcolemmal localization, restoration and reconstitution of the dystrophin-associated protein complex, and improved North Star Ambulatory Assessment (NSAA) total scores that were maintained for 1 year.[6] Herein we report long-term, 4-year safety and functional updates from this study.

## 2 | METHODS

### 2.1 | Study design and participants

Study details have been published elsewhere[6] (see Supporting Information S1). Between November 2017 and April 2018, patients were enrolled at Nationwide Children's Hospital in Columbus, Ohio, USA; 4-year follow-up was completed in April 2022. The trial was approved by the institutional review board of the hospital. Signed informed consent was obtained from participants' parents in compliance with the Code of Federal Regulations (Title 21, Part 50) and International Conference on Harmonization guidelines.

### 2.2 | Study outcomes and assessments

The primary outcome was safety, assessed by adverse events (AEs), changes in laboratory parameters, immunological response to the transgene construct, and reported history and observation of symptoms. Safety data were collected and documented in the electronic case report form. Efficacy outcomes included the NSAA and timed function tests (10-meter walk/run, 100-meter walk/run, four-stair climb, and time to rise) (Table S1). For safety and efficacy outcomes, patients were evaluated at baseline and during follow-up visits (days 1, 7, 14, 30, and 60, and months 3, 6, 9, 12, 18, 24, 30, 36, 42, and 48), with a planned visit at month 54. An increase in NSAA total score and reduction in time to perform timed function tests indicated functional improvement.

### 2.3 | Statistical analysis

Post hoc analyses were conducted to contextualize the data using a propensity-score–weighted external control (EC) cohort, which included patients from the Finding the Optimum Regimen for DMD (FOR-DMD) study.[8–10] Key prognostic factors, including baseline age, NSAA total score, and timed function tests, were used for multivariate, propensity-score weighting, which created a cohort comparable to that of the treatment group (Table S2). Propensity-score–weighting methods are described in Supporting Information S1. SAS software (SAS Institute, Cary, North Carolina) was used to perform the statistical analyses. Missing data were not imputed unless explicitly stated. For NSAA assessments with six or more items missing, the total score was considered as missing data. Incomplete dates (i.e., the exact date an event occurred or ended could not be obtained for the patient) were handled in accordance with the study protocol.

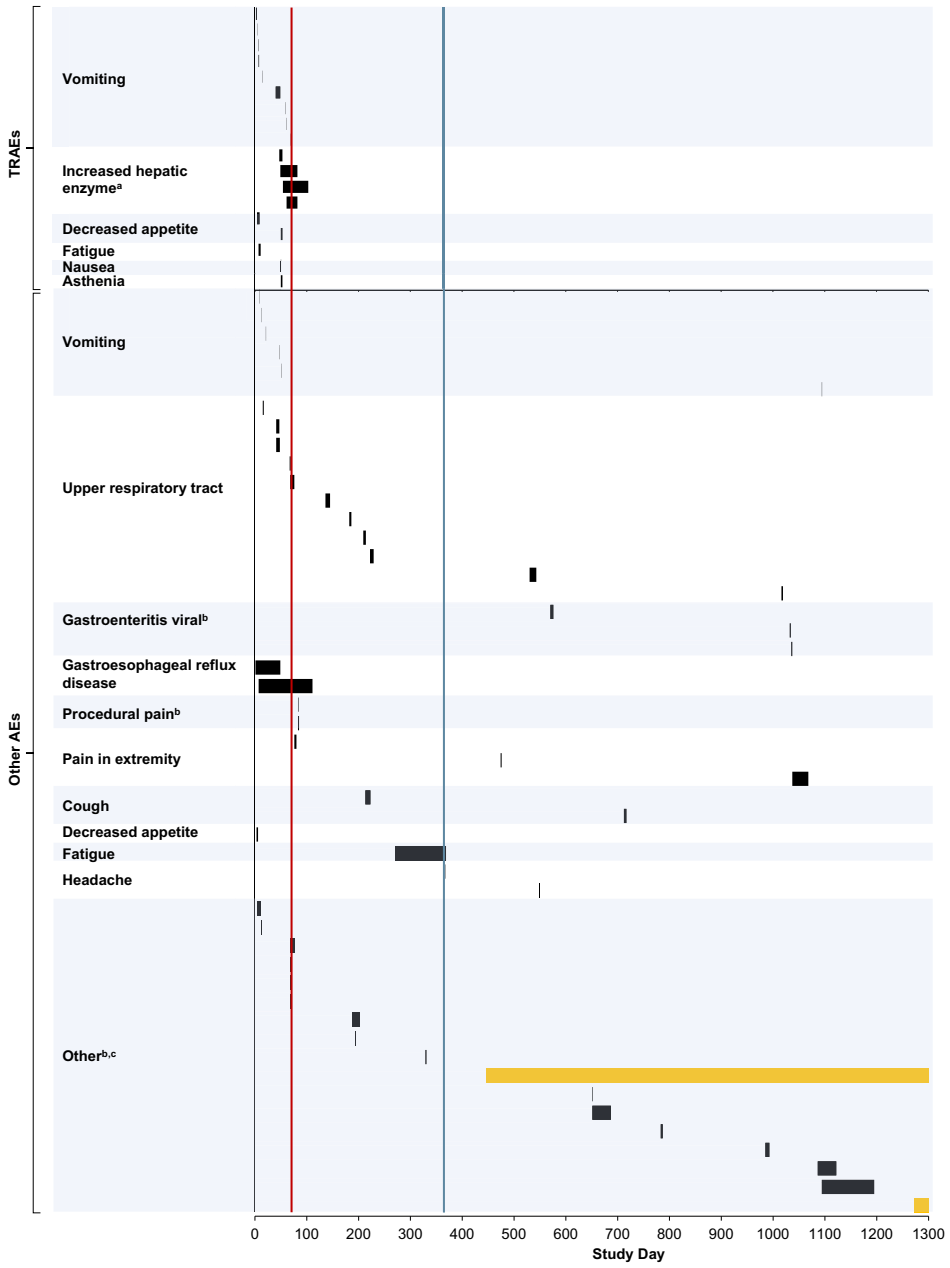
## 3 | RESULTS

### 3.1 | Patients baseline characteristics

Four ambulatory patients with DMD (mean age, 5.1 years) were screened and enrolled (Figure S1). Baseline patient characteristics for the overall population have been described elsewhere (Table S3).[6]

### 3.2 | Safety outcomes

AEs occurring in year 1 posttreatment have been reported.[6] A total of 72 AEs were reported in the current 4-year follow-up analysis. Of the 72 AEs, 18 (25.0%) were treatment-related (TRAEs) (Figure 1). All TRAEs were mild (14 of 18 [77.8%]) or moderate (4 of 18 [22.2%]) in severity, occurred in the first 70 days postinfusion, and resolved. No new TRAEs were reported after 70 days posttreatment. Vomiting and




| TRAEs, *n* (%) | Mild *n* = 14 | Moderate *n* = 4 |
|---|---|---|
| Vomiting | 8 (57.1) | 1 (25.0) |
| Increased hepatic enzyme | 1 (7.1) | 3 (75.0) |
| Decreased appetite | 2 (14.3) | 0 |
| Fatigue | 1 (7.1) | 0 |
| Nausea | 1 (7.1) | 0 |
| Asthenia | 1 (7.1) | 0 |
| **Other AEs, *n* (%)** | **Mild *n* = 26** | **Moderate *n* = 28** |
| Vomiting | 6 (23.1) | 0 |
| Upper respiratory tract infection | 4 (15.4) | 7 (25.0) |
| Gastroenteritis viral[b] | 4 (15.4) | 1 (3.6) |
| Gastroesophageal reflux disease | 0 | 2 (7.1) |
| Procedural pain[b] | 2 (7.7) | 1 (3.6) |
| Pain in extremity | 1 (3.8) | 2 (7.1) |
| Cough | 1 (3.8) | 1 (3.6) |
| Decreased appetite | 1 (3.8) | 0 |
| Fatigue | 0 | 1 (3.6) |
| Headache | 0 | 2 (7.1) |
| Other[b,c] | 7 (26.9) | 11 (39.3) |

**FIGURE 1** Summary of adverse events reported in delandistrogene moxeparvovec–treated patients over 4 years. Onset and duration of TRAEs and other AEs are graphed. Data cut-off was April 26, 2022. Treatment administration occurred on day 0 of the study. The red vertical line indicates day 70. The teal vertical line indicates year 1 posttreatment. Horizontal bars represent the durations of each AE. Yellow bars indicate AEs (skin papilloma and irritability) that were ongoing at the time of data cut-off. See Table S5 for additional information regarding increased hepatic enzymes[a], prior AEs[b], and other AEs[c]. AE, adverse event; TRAE, treatment-related adverse event.

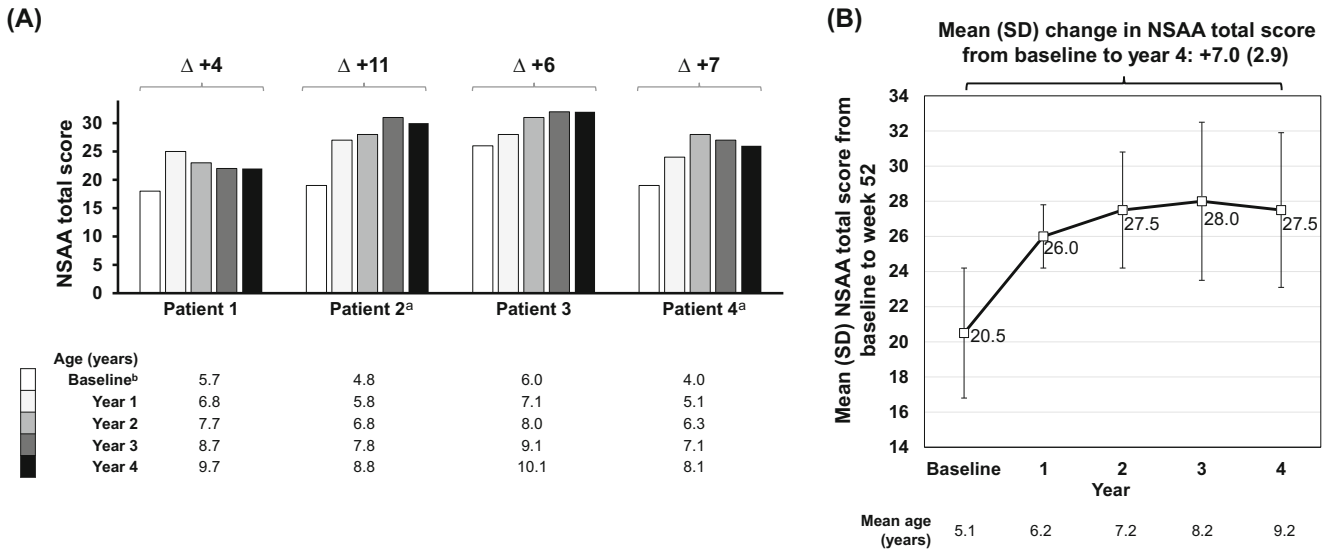



**FIGURE 2** NSAA total scores over 4 years in delandistrogene moxeparvovec–treated patients. (A) NSAA total scores over 4 years in the four patients treated with delandistrogene moxeparvovec. Delta symbols (Δ) denote mean change from baseline to year 4. DMD mutation[7]: patient 1—deletion of exons 46–50; patient 2—deletion of exons 46–49; patient 3—premature stop codon exon 27; patient 4—partial deletion of exon 44. (B) Mean (SD) NSAA total scores from baseline to year 4 after treatment with delandistrogene moxeparvovec. Error bars indicate SD. [a]Patient 2, with 3-year NSAA value, and patient 4, with 2-year NSAA value, were from a remote assessment due to COVID-19–related restrictions at the site. [b]Age at baseline NSAA assessment. COVID-19, coronavirus disease-2019; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

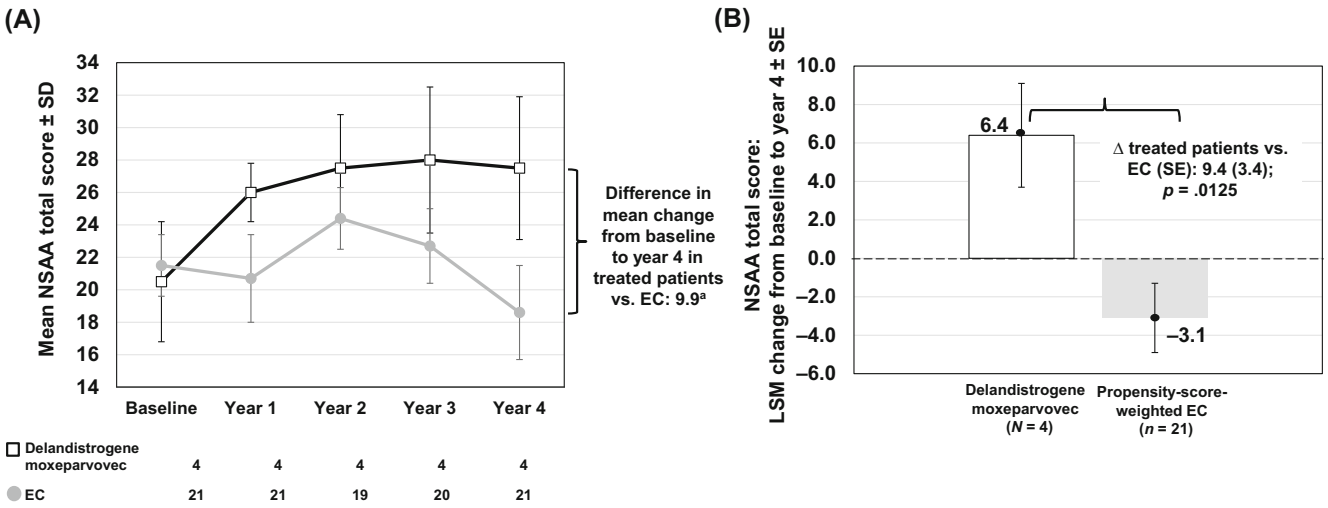



**FIGURE 3** Post hoc analysis. Change from baseline to year 4 in NSAA total score in delandistrogene moxeparvovec–treated patients versus the EC cohort. (A) Mean NSAA total score in delandistrogene moxeparvovec–treated patients versus the EC cohort. (B) NSAA total score LSM change from baseline to year 4 in delandistrogene moxeparvovec–treated patients versus the EC cohort. [a]Calculated using descriptive means, based on propensity-score weighting. EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error.

upper respiratory tract infection occurred in all four patients (100%), while increased hepatic enzyme levels and procedural pain occurred in three of the four patients (75%) (Table S4). Clinically significant abnormalities in serum creatine kinase levels or echocardiogram were not observed. There were no serious AEs or AEs that resulted in study discontinuation. No serious abnormalities were observed in the hematological and chemistry panels, no AEs consistent with complement activation were identified, and no other clinically significant laboratory findings were reported.

### 3.3 | Functional outcomes

Changes from baseline to year 4 in NSAA total score were +4.0, +11.0, +6.0, and +7.0 points in patients 1, 2, 3, and 4, respectively (Figure 2A), with a mean (standard deviation [SD]) of +7.0 (2.9) points (Figure 2B). Mean (SD) change from baseline to year 4 in time to rise, four-stair climb, 100-meter walk/run, and 10-meter walk/run were −0.1 (0.6) second, −1.1 (1.4) seconds, −7.0 (6.0) seconds, and −0.3 (0.5) second, respectively (Figure S2).

### 3.3.1 | Comparison with external control cohort

Delandistrogene moxeparvovec–treated patients showed a sustained increase in NSAA over 4 years, with an unadjusted mean (SD) score of 27.5 (4.4) points versus 18.6 (2.9) in the propensity-score–weighted EC cohort at year 4 (Figure 3A), demonstrating a statistically significant and clinically meaningful difference in change from baseline NSAA (Figure 3B).

## 4 | DISCUSSION

Our findings, after a single, intravenous delandistrogene moxeparvovec administration, demonstrate an acceptable long-term safety profile and sustained, clinically meaningful improvement in motor function. All TRAEs occurred within the first 70 days posttreatment. Assessment of troponin-I and cardiac magnetic resonance imaging were not performed in this study cohort.

In this follow-up study, the average age of patients 4 years posttreatment was 9.2 years, surpassing the mean age at which NSAA decline is expected (6.3 years), as shown by Muntoni and colleagues in a study that demonstrated variability in DMD disease trajectory.[11] Improvements in NSAA were sustained through 4 years and were generally accompanied by improvements in the timed function tests. Importantly, delandistrogene moxeparvovec–treated patients and the EC cohort were rigorously matched to ensure comparability at baseline. Our findings suggest that delandistrogene moxeparvovec leads to a durable and sustained stabilization of motor function over 4 years compared with the pronounced decline predicted by natural history of patients at the same age, managed with corticosteroids, which is the current standard of care.

### 4.1 | Limitations

The use of an open-label, single-center study design with a small sample size is a limitation of our study. In addition, the safety and efficacy of delandistrogene moxeparvovec will need to be monitored continuously over the lifetime of these patients.

## 5 | CONCLUSIONS

In this phase 1/2a study, a single, intravenous administration of delandistrogene moxeparvovec was well tolerated in patients with DMD, with no new safety signals at 4 years posttreatment. Functional assessments demonstrated long-term sustained stabilization of motor function that was clinically meaningful and, importantly, at ages when functional decline is expected based on natural history. In addition, as evidenced by functional results, our study suggests durable expression of delandistrogene moxeparvovec dystrophin protein from an episomal genome in muscle cells.

## AUTHOR CONTRIBUTIONS

**Jerry R. Mendell:** Conceptualization; data curation; formal analysis; funding acquisition; supervision; project administration; resources; writing – original draft; writing – review and editing. **Zarife Sahenk:** Data curation; project administration; resources; writing – review and editing. **Kelly J. Lehman:** Conceptualization; data curation; investigation; project administration; resources; writing – original draft; writing – review and editing. **Linda P. Lowes:** Conceptualization; data curation; writing – review and editing. **Natalie F. Reash:** Conceptualization; data curation; writing – review and editing. **Megan A. Iammarino:** Data curation; writing – original draft; writing – review and editing. **Lindsay N. Alfano:** Conceptualization; data curation; formal analysis; writing – review and editing. **Sarah Lewis:** Data curation; project administration; resources; writing – review and editing. **Kathleen Church:** Conceptualization; project administration; resources; writing – review and editing. **Richard Shell:** Conceptualization; project administration; resources; writing – review and editing. **Rachael A. Potter:** Data curation; project administration; resources; writing – original draft; writing – review and editing. **Danielle A. Griffin:** Data curation; project administration; writing – review and editing. **Mark Hogan:** Data curation; project administration; resources; writing – review and editing. **Shufang Wang:** Data curation; formal analysis; writing – review and editing. **Stefanie Mason:** Data curation; writing – review and editing. **Eddie Darton:** Data curation; writing – review and editing. **Louise R. Rodino-Klapac:** Conceptualization; data curation; funding acquisition; supervision; project administration; resources; writing – original draft; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

J.R.M. reports receiving grants from Parent Project Muscular Dystrophy; receiving personal fees from Sarepta Therapeutics, Inc., and Nationwide Children's Hospital outside the submitted work; and holding a pending patent for a microdystrophin cassette for gene therapy and an issued patent to rAAV.SGCA delivery isolated limb infusion. Z.S. reports receiving grants from Sarepta Therapeutics, Inc., during the conduct of the study. K.J.L. reports receiving grants from Sarepta Therapeutics, Inc., during the conduct of the study. L.P.L. reports receiving grant funding and personal fees from Sarepta Therapeutics, Inc. N.F.R. reports receiving salary support through the Nationwide Children's Hospital from Sarepta Therapeutics, Inc., for training clinical evaluators for upcoming and

ongoing clinical trials. L.N.A. reports receiving royalties and other support for training activities from Sarepta Therapeutics, Inc., via Nationwide Children's Hospital, royalties for licensed technologies, advisory board for Sarepta Therapeutics, Inc., and consultancy for Insmed, Inc., Zogenix, and consultancy services via ATOM International (Amicus Therapeutics, Asklepios Biopharmaceuticals, Biohaven, Edgewise Therapeutics, Italfarmaco) outside the submitted work. S.L., S.W., S.M., E.D., R.A.P., and D.A.G. are employees of Sarepta Therapeutics, Inc. L.R.R.-K. reports receiving personal fees from Myonexus Therapeutics outside the submitted work, holding a patent (pending, licensed, and with royalties paid) to adeno-associated virus delivery of muscle-specific microdystrophin to treat patients with muscular dystrophy, and being an employee of Sarepta Therapeutics, Inc. The remaining authors declare no potential conflicts of interest.

## DATA AVAILABILITY STATEMENT

Qualified researchers may request access to the data that support the findings of this study from Sarepta Therapeutics, Inc., by contacting medinfo@sarepta.com.

## ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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