JAMA Neurology | Original Investigation

Quantitative Muscle Magnetic Resonance Outcomes in Patients With Duchenne Muscular Dystrophy

An Exploratory Analysis From the EMBARK Randomized Clinical Trial

Krista Vandenborne, PhD; Glenn A. Walter, PhD; Volker Straub, PhD; Rebecca J. Willcocks, PhD; Sean C. Forbes, PhD; Eugenio M. Mercuri, MD, PhD; Francesco Muntoni, MD; Kai Ding, PhD; Sravya Ennamuri, MD; Carol Reid, PhD; Alexander P. Murphy, MD, PhD; Marianna Manfrini, MD, PhD; Jerry R. Mendell, MD; Jacob S. Elkins, MD; Louise R. Rodino-Klapac, PhD

IMPORTANCE Delandistrogene moxeparvovec is a recombinant adeno-associated virus rhesus isolate serotype 74 vector-based gene transfer therapy for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed pathogenic variant of the *DMD* gene. In a subset of patients in the EMBARK (A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of Delandistrogene Moxeparvovec [SRP-9001] in Participants With DMD) randomized clinical trial, changes in muscle health and pathology were assessed to evaluate the therapeutic impact of the treatment on disease progression.

OBJECTIVE To determine the effect of delandistrogene moxeparvovec on muscle quantitative magnetic resonance (QMR) measures of disease progression in patients in the EMBARK trial.

DESIGN, SETTING, AND PARTICIPANTS This was a phase 3, double-blind, placebo-controlled (October 2021-September 2023; week 52 cutoff date: September 13, 2023), multicenter randomized clinical trial that included 131 patients. Patients were randomized, and 125 were treated with either delandistrogene moxeparvovec (n = 63) or placebo (n = 62). The current study focused on a subset of patients who underwent muscle QMR imaging.

INTERVENTION Single-administration intravenous delandistrogene moxeparvovec (1.33×10^{14} vector genome/kg) or placebo.

MAIN OUTCOMES AND MEASURES Change from baseline to week 52 in muscle MR was a prespecified exploratory end point. Proton MR spectroscopy (MRS) and 8-point Dixon MR imaging (MRI) measured muscle fat fraction (FF); multislice spin echo MRI measured transverse relaxation time (T_2). MRS FF was measured in the soleus and vastus lateralis. MRI FF and T_2 were measured in 5 leg muscle locations important for ambulation. A post hoc global statistical test combining all muscles and modalities assessed overall treatment effect.

RESULTS In this exploratory EMBARK analysis, 39 male participants (delandistrogene moxeparvovec, n = 19; placebo, n = 20; mean [SD] age, 6.10 [1.04] years; mean [SD] baseline North Star Ambulatory Assessment total score, 22.99 [3.71] points) underwent muscle MRI. Treated patients showed less disease progression vs placebo on MR measures. Across muscles and modalities, magnitudes of FF change favored delandistrogene moxeparvovec; between-group differences in least-squares mean change ranged from −1.01 (95% CI, −2.79 to 0.77; soleus) to −0.71 (95% CI, −3.21 to 1.80; vastus lateralis) for MRS FF and −3.09 (95% CI, −7.62 to 1.45; vastus lateralis) to −0.44 (95% CI, −4.01 to 3.12; hamstrings) for MRI FF. T_2 reductions (improvements; 4 of 5 muscles) were observed in treated patients vs increases (worsening; all muscles) in placebo patients; within-group differences in least-squares mean change ranged from −1.06 (95% CI, −2.10 to −0.02; soleus) to 0.17 (95% CI, −1.76 to 2.10; biceps femoris) in the delandistrogene moxeparvovec group and from 1.12 (95% CI, 0.08-2.16; soleus) to 2.94 (95% CI, 0.84-5.03; quadriceps) in the placebo group. The global statistical test supported treatment benefit (P = .03).

CONCLUSIONS AND RELEVANCE Results reveal that QMR outcomes consistently favored delandistrogene moxeparvovec across muscle groups, with treatment leading to decreased fat accumulation and improved T_2 vs placebo over 52 weeks. Consistent with treatment effects on functional outcomes observed in the EMBARK trial, these results suggest stabilization or less progression of muscle pathology with delandistrogene moxeparvovec—adding to the totality of evidence supporting disease stabilization or slowing of disease progression with delandistrogene moxeparvovec.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05096221

JAMA Neurol. 2025;82(7):734-744. doi:10.1001/jamaneurol.2025.0992
Published online May 12, 2025.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Krista Vandenborne, PhD, Department of Physical Therapy, University of Florida, 101 Newell Dr, Gainesville, FL 32603 (kvandenb@phhp.ufl.edu).

Duchenne muscular dystrophy (DMD) is a rare, X-linked neuromuscular disease caused by pathogenic *DMD* gene variants that result in the absence of functional dystrophin and continuous muscle damage and muscle wasting, beginning from birth.[1] Dystrophin is a 427-kDa cytoskeletal protein required for stability of the sarcolemma, the cell membrane surrounding skeletal and cardiac muscle fibers.[2] In DMD, the absence of functional dystrophin renders muscles susceptible to necrosis and repeated regeneration cycles, diminishing the capacity of muscle cells to regenerate; this ultimately leads to muscle wasting and replacement of muscle with fat and connective tissue.[3] Consequently, patients experience progressive muscle weakness and loss of ambulation, followed by respiratory complications and cardiomyopathy.[4] Some symptomatic and pathogenic variant-specific treatments for DMD are approved[5,6]; however, the unmet need for therapies that can more effectively stabilize or slow the underlying pathologic process has spurred research on innovative treatments, such as gene therapies.

Delandistrogene moxeparvovec is a recombinant adeno-associated virus rhesus isolate serotype 74 (rAAVrh74) vector-based gene transfer therapy that delivers a transgene encoding a microdystrophin, an engineered, functional form of dystrophin shown to stabilize or slow disease progression in DMD.[7-9] It is approved in the US and in other select countries.[10-17] The delandistrogene moxeparvovec transgene was designed to drive targeted expression while mitigating safety concerns,[7] with the MHCK7 promoter and enhancer driving expression in skeletal muscle (including the diaphragm) and the heart while minimizing off-target expression.[7,18]

The EMBARK (A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of Delandistrogene Moxeparvovec [SRP-9001] in Participants With DMD) trial was a large (N = 125), phase 3, multinational, placebo-controlled randomized clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec in ambulatory patients with DMD 4 years and older to younger than 8 years.[9,19] In part 1 (week 52), stabilization or slowing of disease progression and manageable safety were observed after delandistrogene moxeparvovec treatment,[9] consistent with early-phase trials.[8,20-22] Although the study did not meet the primary end point (change from baseline to week 52 in the North Star Ambulatory Assessment [NSAA]), key secondary functional end points, including time to rise (TTR) and 10-m walk/run test, favored delandistrogene moxeparvovec.[9]

A subset of patients from participating EMBARK study sites underwent muscle magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI), which were prespecified exploratory end points. MR is a noninvasive method to monitor DMD progression,[23] and quantitative MR (QMR) measures of muscle pathology, particularly those capturing the replacement of muscle with fat, are highly promising DMD biomarkers.[24] QMR measures can be used to assess therapeutic responses and are valuable adjuncts to clinical assessments due to their sensitivity to subclinical disease progression and lack of dependence on participant growth, maturation, and motivation.[25] Additionally, alterations in muscle MR show quantifiable changes earlier than clinical outcomes.[24] QMR changes become more pronounced with aging, first manifesting in proximal muscle groups and later progressing to distal muscles.[26,27] QMR changes in the proximal vastus lateralis and biceps femoris (lower extremity muscle groups) are well defined and highly responsive to disease progression in ambulatory patients with DMD.[24] We present muscle MR data—including proton MRS and 8-point Dixon MRI to determine fat fraction (FF), as well as multislice spin echo MRI to measure transverse relaxation time (T_2)—from patients with MR data participating in the EMBARK trial part 1.

Key Points

Question How can quantitative magnetic resonance (QMR) measures be used to evaluate the efficacy of delandistrogene moxeparvovec vs placebo for the treatment of patients with Duchenne muscular dystrophy (DMD)?

Findings In a subset of 39 patients with DMD who underwent muscle QMR imaging in part 1 (week 52) of the phase 3 EMBARK randomized clinical trial (A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of Delandistrogene Moxeparvovec [SRP-9001] in Participants With DMD), those treated with delandistrogene moxeparvovec showed less disease progression in lower extremity muscles vs patients treated with placebo.

Meaning Based on muscle QMR measures, results reveal that delandistrogene moxeparvovec appeared to demonstrate efficacy in protecting muscle from progressive damage, resulting in less fat accumulation in muscles over time.

Methods

EMBARK Trial

The EMBARK trial was approved by the central institutional review board, Advarra, and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all legal guardians of minor participants before performing any procedures required for this study in compliance with all applicable guidelines. Details on EMBARK study design, safety, and primary efficacy findings have been previously published; the protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively.[9] Briefly, the phase 3, 2-part EMBARK trial evaluated the efficacy and safety of delandistrogene moxeparvovec in 125 ambulatory patients with DMD. In part 1 (52 weeks), patients were randomized 1:1 to receive delandistrogene moxeparvovec (1.33×10^{14} vector genome/kg by linear standard quantitative polymerase chain reaction) or placebo. In part 2 (52 weeks), patients who received placebo in part 1 received delandistrogene moxeparvovec and those treated with delandistrogene moxeparvovec in part 1 received placebo. Patients in the EMBARK trial met the following inclusion criteria: (1) ambulatory and 4 years or older to younger than 8 years, (2) definitive DMD diagnosis (pathogenic *DMD* variant fully contained between exons 18 and 79 [inclusive]), (3) able to cooperate with motor assessments, (4) NSAA total score

greater than 16 and less than 29, (5) TTR from the floor less than 5 seconds, (6) stable daily oral corticosteroid dose for 12 or more weeks (corticosteroid dosing and dosing duration were generally balanced between groups throughout the study [eTable in Supplement 3]), and (7) rAAVrh74 antibody titers not elevated. EMBARK trial exclusion criteria were (1) exposure to gene therapy or treatment designed to increase dystrophin expression, (2) abnormality in laboratory tests, and (3) any clinically significant condition or requirement for chronic treatment creating unnecessary risk for gene transfer. Other inclusion and exclusion criteria applied. Racial and ethnic demographic questions were self-reported, and the 2-question format and categories used were consistent with US Food and Drug Administration guidance. Race categories included Asian, Black or African American, multiracial, White, other (which included Native Hawaiian or Other Pacific Islander), and not reported. Ethnicity categories included Hispanic or Latino, not Hispanic or Latino, and not reported/unknown. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

The primary end point was change from baseline to week 52 in NSAA total score. Key secondary end points were quantity of microdystrophin expression at week 12 (Western blot), change from baseline to week 52 in TTR from the floor, and change from baseline to week 52 in 10-m walk/run test.

MR Protocols

In the EMBARK trial part 1, a prespecified exploratory efficacy end point of change in muscle MRI findings from baseline over 52 weeks evaluated the therapeutic impact of delandistrogene moxeparvovec on MR biomarkers of disease progression in a subset of participants who underwent muscle QMRI (eFigure 1 in Supplement 3). Participating sites were preselected based on experience performing QMRI. All patients at these preselected sites participated in the MRI substudy; no further randomization was done. Muscle QMRI was conducted at baseline and week 52 using a Philips or Siemens 3-T system. The study was not powered for statistical testing of MR parameters.

Protocols included proton MRS, 8-point Dixon MRI, and multislice spin echo imaging (T_2). Localized proton MRS (stimulated echo acquisition mode) was used to measure muscle FF in the soleus and vastus lateralis (muscles important for lower limb function). Eight-point Dixon MRI, which exploits the chemical shift difference in water and fat to produce high-resolution water and fat images,[28] was used to quantify FF in 5 preselected lower leg and thigh muscles and muscle groups with important roles in ambulation: the biceps femoris (long head), hamstrings (semitendinosus, semimembranosus, biceps femoris), quadriceps (rectus femoris, vastus intermedius, vastus lateralis, vastus medialis), soleus, and vastus lateralis.[29,30] Biceps femoris and vastus lateralis data are presented individually due to their importance in DMD. Multislice spin echo imaging was implemented to create quantitative T_2 maps and to measure mean T_2 values (sensitive to changes in FF and muscle damage, inflammation, and edema) in the same 5 muscles.[31-34]

Statistical Analyses

For each QMR measure, a descriptive summary of changes from baseline, including unadjusted means (SEs), overall change, and results stratified by age group, as well as baseline and week 52 values, is presented.

Adjusted least-squares mean (LSM) differences by muscle location or group and MR parameter were calculated via an analysis of covariance with covariates for treatment and baseline value. Because the primary end point was not met and subsequent CIs in the hierarchy were not adjusted for multiplicity, LSM changes and 95% CIs (unadjusted for multiplicity) are presented with nominal *P* values.

A post hoc global statistical test (GST; Wei-Lachin test), which controls for multiplicity by reducing all measured parameters into a single test,[35] was applied to evaluate the overall delandistrogene moxeparvovec treatment effect across muscle groups and imaging modalities. The GST tested the null hypothesis of no treatment difference in all 12 muscle parameters. Permutation tests (n = 100 000) were stratified within baseline age group to maintain balance between the 2 treatment arms. Data were analyzed using SAS software, version 9.4 (SAS Institute).

Results

Participants

A total of 39 male participants (mean [SD] age, 6.10 [1.04] years) in the EMBARK trial (delandistrogene moxeparvovec, n = 19; placebo, n = 20) underwent muscle MRI. Among these patients, the mean (SD) baseline NSAA total score was 22.99 (3.71) points. Demographics and baseline clinical characteristics were balanced between groups (**Table 1**). Patients self-reported the following races: 3 Asian (7.69%), 1 multiracial (2.56%), 34 White (87.18%), and 1 not reported (2.56%). Patients self-reported the following ethnicities: 10 Hispanic or Latino (25.64%) and 29 not Hispanic or Latino (74.36%).

MRS FF

Table 2 shows MRS FF results at baseline and week 52, in addition to within- and between-group differences for LSM change from baseline to week 52. Across both muscles, the delandistrogene moxeparvovec group had a smaller increase (worsening) in MRS-measured muscle FF than the placebo group (**Figure 1**A). In the soleus, the mean (SE) change from baseline to week 52 in MRS FF was 0.28% (0.28%) in the delandistrogene moxeparvovec group and 1.17% (0.80%) in the placebo group (Figure 1A). In the vastus lateralis, these changes were 0.86% (0.83%) and 2.07% (0.97%), respectively. Between-group differences in LSM change ranged from −1.01 (95% CI, −2.79 to 0.77; soleus) to −0.71 (95% CI, −3.21 to 1.80; vastus lateralis). Analyses of within-group LSM changes from baseline to week 52 (Table 2) in the placebo group yielded *P* values ≤.05 for increases in both muscles (Table 2). For all other within-group and all between-group differences, *P* values were >.05.

MRI FF

Table 2 shows MRI FF results at baseline and week 52 in addition to within- and between-group comparisons of LSM

Table 1. Demographics and Baseline Clinical Characteristics

Characteristic[a]	Delandistrogene moxeparvovec (n = 19)	Placebo (n = 20)	All (N = 39)
Age, mean (SD), y	5.92 (1.10)	6.27 (0.98)	6.10 (1.04)
4-5 y, No. (%)	10 (52.63)	9 (45.00)	19 (48.72)
6-7 y, No. (%)	9 (47.37)	11 (55.00)	20 (51.28)
Race, No. (%)			
Asian	1 (5.26)	2 (10.00)	3 (7.69)
Black or African American	0	0	0
Multiracial	1 (5.26)	0	1 (2.56)
White	16 (84.21)	18 (90.00)	34 (87.18)
Other[b]	0	0	0
Not reported	1 (5.26)	0	1 (2.56)
Ethnicity, No. (%)			
Hispanic or Latino	6 (31.58)	4 (20.00)	10 (25.64)
Not Hispanic or Latino	13 (68.42)	16 (80.00)	29 (74.36)
Not reported/unknown	0	0	0
Dosing weight, mean (SD), kg	22.44 (6.31)	21.77 (5.94)	22.09 (6.05)
Time since corticosteroid treatment started, mean (SD), y	0.77 (0.53)	0.91 (0.51)	0.84 (0.52)
Pathogenic variant, No. (%)			
Large deletion	16 (84.21)	13 (65.00)	29 (74.36)
Large duplication	0	0	0
Small pathogenic variant	3 (15.79)	7 (35.00)	10 (25.64)
NSAA total score, mean (SD), points	23.61 (3.85)	22.40 (3.58)	22.99 (3.71)
TTR, mean (SD), s	3.48 (0.98)	3.46 (0.78)	3.47 (0.87)
10MWR, mean (SD), s	4.46 (0.60)	5.05 (0.75)	4.76 (0.73)
SV95C, mean (SD), m/s	1.83 (0.30)	1.77 (0.26)	1.80 (0.28)
100MWR, mean (SD), s	55.97 (9.98)	61.60 (18.45)	58.79 (14.91)
Time to ascend 4 steps, mean (SD), s	2.77 (0.55)	3.46 (0.92)	3.12 (0.83)

Abbreviations: 10MWR, 10-m walk/run; 100MWR, 100-m walk/run; MR, magnetic resonance; NSAA, North Star Ambulatory Assessment; SV95C, stride velocity 95th centile; TTR, time to rise.

[a] Only a subset of EMBARK study participants underwent MR assessments. Participating sites were preselected based on experience performing quantitative MR imaging; all patients at these preselected sites participated in the MR imaging substudy and no further randomization was conducted.

[b] Other race includes Native Hawaiian or Other Pacific Islander.

change from baseline to week 52. The delandistrogene moxeparvovec group exhibited smaller increases in MRI FF than the placebo group across muscle locations (Figure 1B). The mean (SE) changes from baseline to week 52 in the delandistrogene moxeparvovec group vs the placebo group were 1.67% (1.44%) vs 3.67% (1.85%) for the biceps femoris, 0.76% (1.23%) vs 1.17% (1.15%) for the hamstrings, 0.55% (0.91%) vs 3.32% (1.99%) for the quadriceps, −0.65% (0.82%) vs 0.45% (0.91%) for the soleus, and 0.72% (0.93%) vs 3.89% (2.14%) for the vastus lateralis (Figure 1B). Between-group differences in LSM change ranged from −3.09 (95% CI, −7.62 to 1.45; vastus lateralis) to −0.44 (95% CI, −4.01 to 3.12; hamstrings). Analyses of within-group LSM changes from baseline to week 52 (Table 2) in the placebo group showed *P* values ≤.05 for increases in the biceps femoris, quadriceps, and vastus lateralis. All other within-group and all between-group comparisons yielded *P* values >.05. Figure 1C shows Dixon MRI FF maps at baseline and week 52 in 2 patients (1 in the delandistrogene moxeparvovec group and 1 in the placebo group) who had similar baseline vastus lateralis fat fraction values.

MRI T_2

Table 2 shows MRI T_2 results at baseline and week 52 and within- and between-group differences for LSM change from baseline to week 52. The treatment group showed a T_2 decrease (improvement) in 4 of 5 muscle regions, whereas the placebo group showed an increase (worsening) across all 5 muscle locations (Figure 1D). The mean (SE) changes from baseline to week 52 in the delandistrogene moxeparvovec group vs the placebo group were 0.05 (0.71) milliseconds vs 2.46 (0.92) milliseconds for biceps femoris, −0.89 (0.66) milliseconds vs 1.52 (0.91) milliseconds for hamstrings, −0.43 (0.93) milliseconds vs 3.02 (1.12) milliseconds for quadriceps, −1.05 (0.42) milliseconds vs 1.11 (0.58) milliseconds for soleus, and −0.50 (0.85) milliseconds vs 2.90 (1.09) milliseconds for vastus lateralis (Figure 1D). Analyses of within-group differences in LSM change ranged from −1.06 (95% CI, −2.10 to −0.02; soleus) to 0.17 (95% CI, −1.76 to 2.10; biceps femoris) in the delandistrogene moxeparvovec group and from 1.12 (95% CI, 0.08-2.16; soleus) to 2.94 (95% CI, 0.84-5.03; quadriceps) in the placebo group. Analyses of within-group LSM change from baseline to week 52 (Table 2) in the placebo group yielded *P* values ≤.05 for increases in all muscle locations. Within-group analyses in the delandistrogene moxeparvovec group showed a *P* value of .05 for a decrease in the soleus. Between-group differences in LSM change from baseline to week 52 were −3.26 (95% CI, −6.41 to −0.10; *P* = .04) for the quadriceps, −2.18 (95% CI, −3.65 to −0.70; *P* = .01) for the soleus, and −3.31 (95% CI, −6.39 to −0.24; *P* = .04) for the vastus lateralis. All other within- and between-group comparisons yielded *P* values >.05.

Table 2. Magnetic Resonance (MR) End Points by Muscle/Muscle Group at Baseline and Week 52[a]

Variable	Soleus		Vastus lateralis		Biceps femoris	
	Delandistrogene moxeparvovec	Placebo	Delandistrogene moxeparvovec	Placebo	Delandistrogene moxeparvovec	Placebo
MRS FF, %						
Baseline						
No.	16	17	15	17	NA	NA
Mean (SE)	5.66 (0.85)	4.36 (0.59)	5.53 (0.84)	8.61 (2.44)	NA	NA
Week 52						
No.	17	17	15	16	NA	NA
Mean (SE)	5.83 (0.80)	5.74 (1.06)	6.47 (1.16)	10.46 (3.19)	NA	NA
Change within group						
LSM (95% CI)	0.22 (−1.00 to 1.44)	1.23 (−0.03 to 2.49)	1.13 (−0.69 to 2.95)	1.84 (0.14 to 3.53)	NA	NA
P value	.71	.05	.21	.03	NA	NA
Change vs placebo						
LSM (95% CI)	−1.01 (−2.79 to 0.77)	NA	−0.71 (−3.21 to 1.80)	NA	NA	NA
P value	.25	NA	.57	NA	NA	NA
MRI FF, %						
Baseline						
No.	16	17	15	16	15	16
Mean (SE)	9.26 (0.98)	7.63 (0.63)	9.86 (1.14)	9.83 (1.86)	11.03 (0.82)	14.93 (3.84)
Week 52						
No.	17	17	16	17	17	17
Mean (SE)	8.63 (0.95)	8.34 (1.04)	10.68 (1.44)	13.52 (2.99)	12.65 (1.48)	17.31 (4.78)
Change within group						
LSM (95% CI)	−0.52 (−2.28 to 1.24)	0.31 (−1.52 to 2.13)	0.76 (−2.45 to 3.97)	3.85 (0.64 to 7.06)	2.18 (−0.73 to 5.08)	3.12 (0.12 to 6.13)
P value	.56	.73	.63	.02	.14	.04
Change vs placebo						
LSM (95% CI)	−0.82 (−3.39 to 1.74)	NA	−3.09 (−7.62 to 1.45)	NA	−0.95 (−5.16 to 3.26)	NA
P value	.52	NA	.17	NA	.65	NA
MRI T_2, millisecond						
Baseline						
No.	15	17	13	18	13	18
Mean (SE)	40.51 (0.91)	40.82 (0.88)	40.85 (0.94)	42.36 (1.02)	42.32 (0.62)	45.64 (1.76)
Week 52						
No.	17	17	15	16	15	16
Mean (SE)	39.39 (0.80)	42.08 (1.03)	39.84 (0.60)	45.38 (1.81)	41.77 (0.60)	48.11 (2.21)
Change within group						
LSM (95% CI)	−1.06 (−2.10 to −0.02)	1.12 (0.08 to 2.16)	−0.45 (−2.73 to 1.82)	2.86 (0.83 to 4.89)	0.17 (−1.76 to 2.10)	2.36 (0.64 to 4.08)
P value	.05	.04	.69	.01	.86	.01
Change vs placebo						
LSM (95% CI)	−2.18 (−3.65 to −0.70)	NA	−3.31 (−6.39 to −0.24)	NA	−2.19 (−4.83 to 0.44)	NA
P value	.01	NA	.04	NA	.10	NA

(continued)

MR Results by Age Subgroup

Across most muscle regions of interest and MR end points, the mean change from baseline to week 52 favored treatment in both age subgroups, with a greater treatment difference in the 6- to 7-year-old subgroup (**Figure 2** and **Figure 3**). In 6- to 7-year-old patients, the delandistrogene moxeparvovec group had smaller increases in MRS FF in both muscles vs the placebo group (Figure 2A). For MRI FF, the delandistrogene moxeparvovec group generally showed greater reductions (soleus [4- to 5-year-old patients]), reductions vs increases (quadriceps and vastus lateralis [6- to 7-year-old patients]), or smaller increases (quadriceps and vastus lateralis [4- to 5-year-old patients]; biceps femoris and hamstrings [6- to 7-year-old patients]) compared with the placebo group in both age subgroups (Figure 2B). The delandistrogene moxeparvovec group showed a T_2 decrease in all muscles in the 4- to 5-year-old sub-

Table 2. Magnetic Resonance (MR) End Points by Muscle/Muscle Group at Baseline and Week 52[a] (continued)

Variable	Soleus		Vastus lateralis		Biceps femoris	
	Delandistrogene moxeparvovec	Placebo	Delandistrogene moxeparvovec	Placebo	Delandistrogene moxeparvovec	Placebo
	Hamstrings			Quadriceps		
	Delandistrogene moxeparvovec		Placebo	Delandistrogene moxeparvovec		Placebo
MRS FF, %						
Baseline						
No.	NA		NA	NA		NA
Mean (SE)	NA		NA	NA		NA
Week 52						
No.	NA		NA	NA		NA
Mean (SE)	NA		NA	NA		NA
Change within group						
LSM (95% CI)	NA		NA	NA		NA
P value	NA		NA	NA		NA
Change vs placebo						
LSM (95% CI)	NA		NA	NA		NA
P value	NA		NA	NA		NA
MRI FF, %						
Baseline						
No.	15		16	15		16
Mean (SE)	12.85 (0.84)		13.64 (1.71)	11.53 (1.09)		10.99 (1.77)
Week 52						
No.	17		17	16		17
Mean (SE)	13.75 (1.21)		14.68 (1.99)	12.32 (1.42)		14.11 (2.84)
Change within group						
LSM (95% CI)	0.74 (−1.73 to 3.21)		1.19 (−1.37 to 3.75)	0.47 (−2.50 to 3.45)		3.40 (0.42 to 6.37)
P value	.54		.35	.75		.03
Change vs placebo						
LSM (95% CI)	−0.44 (−4.01 to 3.12)		NA	−2.93 (−7.14 to 1.28)		NA
P value	.80		NA	.16		NA
MRI T_2, millisecond						
Baseline						
No.	13		18	13		18
Mean (SE)	42.77 (0.60)		44.44 (1.05)	42.27 (0.89)		43.47 (1.02)
Week 52						
No.	15		16	15		16
Mean (SE)	41.40 (0.63)		46.01 (1.49)	41.25 (0.65)		46.65 (1.91)
Change within group						
LSM (95% CI)	−0.90 (−2.76 to 0.96)		1.52 (−0.14 to 3.18)	−0.32 (−2.66 to 2.02)		2.94 (0.84 to 5.03)
P value	.33		.07	.78		.01
Change vs placebo						
LSM (95% CI)	−2.42 (−4.94 to 0.10)		NA	−3.26 (−6.41 to −0.10)		NA
P value	.06		NA	.04		NA

Abbreviations: FF, fat fraction; LSM, least-squares mean; MRI, MR imaging; MRS, MR spectroscopy; NA, not available/applicable; T_2, transverse relaxation time.

[a] Cutoff date: September 13, 2023.

group and in 3 of 5 muscles (hamstrings, soleus, and vastus lateralis) in the 6- to 7-year-old subgroup; the placebo group showed an increase across all 5 muscles in both age subgroups (Figure 3).

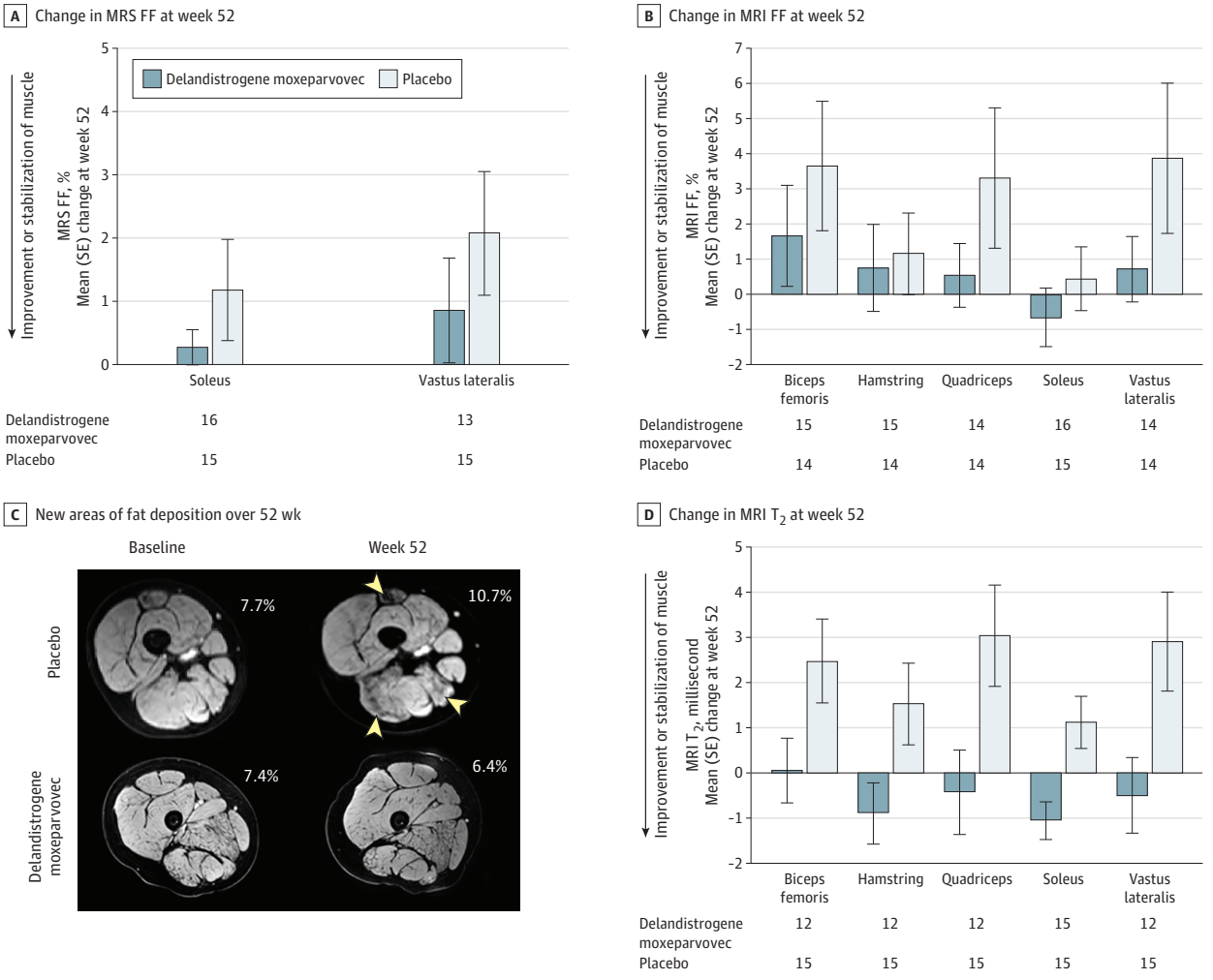
GST Combining Muscle Locations

The GST yielded a *P* value of .03, favoring delandistrogene moxeparvovec across the 12 MR parameters.

Discussion

In patients with muscular dystrophies, including DMD, skeletal muscle is affected by inflammation, edema, necrosis, atrophy, and hypertrophy and is progressively replaced with fat. Quantitative muscle MR measures, such as MRS FF, MRI FF, and MRI T_2, can be used to detect inflammation,

Figure 1. Change in Magnetic Resonance (MR) End Points at Week 52 (EMBARK Part 1)



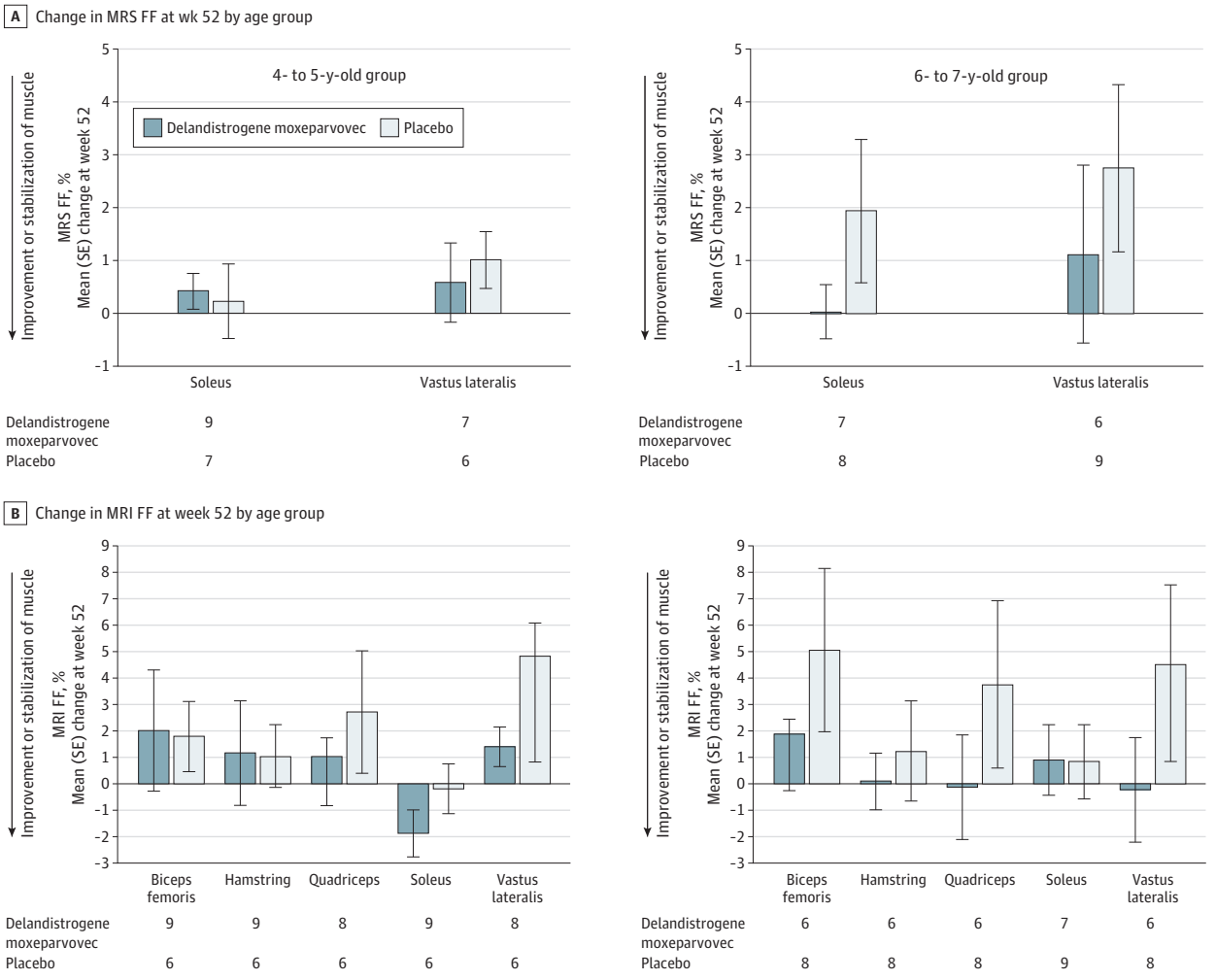
A, Change in MR spectroscopy (MRS) fat fraction (FF) at week 52 (EMBARK part 1). B, Change in MR imaging (MRI) FF at week 52 (EMBARK part 1); Dixon water images of the upper leg at baseline and week 52 in 2 patients (1 in the delandistrogene moxeparvovec group and 1 in the placebo group) who had similar FF values in the vastus lateralis at baseline. C, Arrowheads indicate new areas of fat deposition over 52 weeks. D, Change in MRI transverse relaxation time (T_2) at week 52 (EMBARK part 1). Data are presented for patients with values at both baseline and week 52. Cutoff date: September 13, 2023.

edema, and replacement of muscle tissue with fat, making them important tools for diagnosing and monitoring disease progression.[32,36,37] MRI measures can noninvasively reveal muscle pathology changes throughout disease progression and can be integrated with clinical assessments to comprehensively and objectively investigate therapeutic impact and disease progression after treatment.[6,23,37,38]

In the EMBARK trial, exploratory MR end points included MRS- and 8-point Dixon MRI-measured FF and MRI T_2. FF is a reliable biomarker of muscle tissue replacement with fat and increases with age and DMD disease progression.[26] FF in the vastus lateralis is predictive of loss of ambulation in DMD.[29] Muscle T_2 increases with increased FF, muscle damage, inflammation, and edema and is elevated in boys with DMD.[33] Elevated T_2 values are present even at young ages and when functional assessments are stable,[32,34] with changes in T_2 often preceding those in FF.

Overall, MR outcomes in the EMBARK trial indicated worsening muscle health in patients treated with placebo vs stabilization or slowing of disease progression in patients treated with delandistrogene moxeparvovec over the 52-week follow-up period. Results were generally consistent across muscle locations and MR parameters and aligned with findings from a previous MRI study[25] of 3 patients treated with delandistrogene moxeparvovec (mean age: 6.8 years), which reported minimal fat accumulation in treated patients vs an age-matched natural history cohort (mean age: 6.8 years) 6 to 24 months after treatment. MRI changes in the EMBARK trial were congruent with functional outcomes from the EMBARK trial part 1 showing disease stabilization or slowing of disease progression in patients treated with delandistrogene moxeparvovec and progression in patients treated with placebo, demonstrating treatment efficacy (functional outcomes in participants from the MR substudy are shown in eFigure 2

Figure 2. Change in Magnetic Resonance Spectroscopy (MRS) Fat Fraction (FF) and MR Imaging (MRI) FF From Baseline to Week 52 (EMBARK Part 1) by Age Group



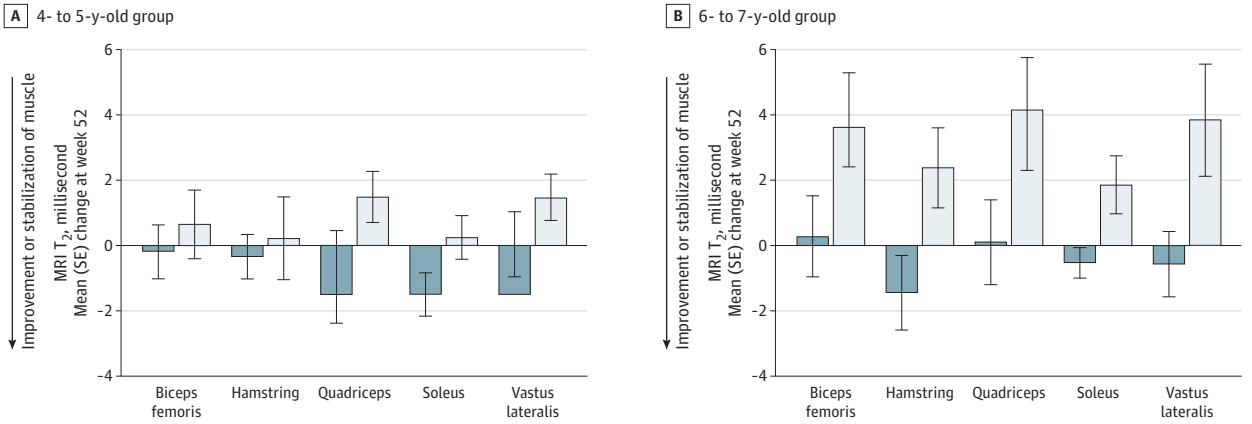
A, Change in MRS FF at week 52 by age group. B, Change in MRI FF (%) at week 52 by age group. Data are presented for patients with values at both baseline and week 52. Cutoff date: September 13, 2023.

in Supplement 3).[9] Given the short observation period (52 weeks) and slow progression of DMD in children at the ages studied (≥4 to <8 years), these effects would likely become increasingly prominent over time.

Across all studied muscles in the EMBARK trial, the magnitudes of change from baseline to week 52 in MRS FF and MRI FF in the delandistrogene moxeparvovec group vs the placebo group, although not statistically significant, were reduced, indicating less fat accumulation in muscle with delandistrogene moxeparvovec. Discrepancies in the significance of T_2 changes vs FF changes may be attributed to earlier changes in T_2 vs FF in DMD, as reported previously,[32] and compounded by the small sample size and short follow-up duration. MR changes in the vastus lateralis (MRS FF and T_2) and biceps femoris (T_2) may be particularly sensitive to disease progression in ambulatory patients with DMD,[39] and these muscles (in addition to the quadriceps) accordingly showed the greatest increases (worsening) in MR measures in the placebo group but not the delandistrogene moxeparvovec group. Given the relationship between vastus lateralis FF and ambulation loss in DMD,[29] these findings highlight the potential clinical importance of the delandistrogene moxeparvovec treatment benefit.

In treated patients from the EMBARK trial, MR T_2 was reduced from baseline in 4 of the 5 muscle groups, suggesting likely improvement in muscle integrity. The placebo group, by contrast, worsened (T_2 increased) across all studied muscle regions. In keeping with the literature and the ages studied, T_2—indicative of early detectable inflammation as well as replacement of muscle tissue with fat in younger patients with DMD—demonstrated greater sensitivity than FF in the EMBARK trial. The stronger treatment effect on T_2 vs FF measures was evident in the quadriceps and vastus lateralis, proximal muscle groups that are affected earlier in the disease course than distal muscles.[33] Group differences in LSM changes in T_2 for

Figure 3. Change in Magnetic Resonance Imaging (MRI) Transverse Relaxation Time (T_2) From Baseline to Week 52 (EMBARK Part 1) by Age Group



A, Group aged 4 to 5 years. B, Group aged 6 to 7 years. Data are presented for patients with values at both baseline and week 52. Cutoff date: September 13, 2023.

the quadriceps, soleus, and vastus lateralis further highlighted this effect.

Analyses stratified by age subgroup showed greater worsening in the 6- to 7-year-old patients treated with placebo. The observed differences between placebo and delandistrogene moxeparvovec groups (ie, the treatment effect) were also greater in the 6- to 7-year-old patients across end points, which is perhaps unsurprising given that these measures reportedly increase with age in untreated patients with DMD. In the 4- to 5-year-old patients treated with placebo, increases in MR outcomes were minimal in the soleus, the most distal muscle region studied, aligning with research showing that proximal regions are the earliest affected in DMD.[26,27]

Results of the GST, which was used to analyze a composite end point spanning all muscle regions and MR parameters in the study, further supported the individual MR results, indicating that the congruent observations across muscle regions and MR parameters were not an artifact of multiple testing. These results align with those from the EMBARK trial part 1 GST comprising 6 functional end points, which showed a delandistrogene moxeparvovec treatment effect after accounting for multiple hypotheses tested across the primary and secondary end points.[9] A GST can be used to assess multiple clinically relevant outcomes and overcome the potential hurdles of artificially selecting a single outcome.[35] For example, if a primary study outcome improves but secondary outcomes decline, the primary outcome effect may be misleading. Similarly, if the primary outcome does not meet significance thresholds but the secondary outcomes do, a GST can combine trends to reflect overall improvement.

In keeping with functional changes in secondary end points observed in the EMBARK trial part 1, these exploratory EMBARK MR findings provide evidence that delandistrogene moxeparvovec microdystrophin resulted in improved muscle membrane stability and reduced fat accumulation over time.[1]

Limitations

A key limitation of this study was the small sample size of MR assessments in the EMBARK trial, which may not provide enough power to detect all possible treatment effects. Additionally, the study was not powered for statistical testing of the exploratory MR outcomes, and the selection of sites conducting MRI was not randomized. A further consideration is the challenge associated with MRI scans in young children, whose muscles may show only small changes that are difficult to detect compared with those in older children. Finally, it is important to consider the potential influence of corticosteroid use, as patients with DMD who use corticosteroids have been shown to have lower MR T_2 values than steroid-naive patients over 52 weeks.[40] Notably, all patients in the EMBARK trial received corticosteroids before and after baseline, and the duration and dosing in patients in the MR substudy were generally balanced across the study (eTable in Supplement 3). It is, thus, unlikely that our findings could be attributed to differences in corticosteroid use.

Conclusions

These exploratory, hypothesis-generating MR findings from the EMBARK randomized clinical trial part 1 require confirmation in a future randomized controlled trial testing a clinically relevant end point. Findings were congruent with results for secondary functional outcomes in the EMBARK trial[9]; MR results were generally consistent across muscle locations and MR sequences, suggesting that delandistrogene moxeparvovec may sustain muscle health and reduce muscle wasting. This work adds to the totality of evidence supporting stabilization or slowing of disease progression with delandistrogene moxeparvovec. Given that FF has been linked to loss of ambulation in DMD[29] and these MRI/

MRS findings align with EMBARK trial group differences (delandistrogene moxeparvovec vs placebo) in progression to the 5-second TTR threshold prognostic of significant ambulation loss,[9,41,42] these results may have implications for the preservation of ambulation in patients with DMD treated with delandistrogene moxeparvovec.

ARTICLE INFORMATION

Accepted for Publication: January 31, 2025.

Published Online: May 12, 2025. doi:10.1001/jamaneurol.2025.0992

Author Affiliations: Department of Physical Therapy, University of Florida, Gainesville (Vandenborne, Willcocks, Forbes); Department of Physiology and Aging, University of Florida, Gainesville (Walter); John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom (Straub); Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy (Mercuri); The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health and Institute of Neurology, University College London, & Great Ormond Street Hospital Trust, London, United Kingdom (Muntoni); Sarepta Therapeutics Inc, Cambridge, Massachusetts (Ding, Ennamuri, Mendell, Elkins, Rodino-Klapac); Roche Products Ltd, Welwyn Garden City, United Kingdom (Reid, Murphy); F. Hoffmann-La Roche Ltd, Basel, Switzerland (Manfrini); Center for Gene Therapy, Nationwide Children's Hospital, Columbus, Ohio (Mendell); The Ohio State University, Columbus (Mendell).

Author Contributions: Drs Ennamuri and Ding had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Vandenborne, Willcocks, Murphy, Elkins, Rodino-Klapac.
Acquisition, analysis, or interpretation of data: Vandenborne, Walter, Straub, Willcocks, Forbes, Mercuri, Muntoni, Ding, Ennamuri, Reid, Manfrini, Mendell, Rodino-Klapac.
Drafting of the manuscript: Vandenborne, Forbes, Muntoni, Ding, Ennamuri, Reid, Murphy, Elkins, Rodino-Klapac.
Critical review of the manuscript for important intellectual content: Vandenborne, Walter, Straub, Willcocks, Forbes, Mercuri, Muntoni, Ding, Ennamuri, Reid, Murphy, Manfrini, Mendell, Rodino-Klapac.
Statistical analysis: Ding, Reid.
Administrative, technical, or material support: Walter, Forbes, Ennamuri, Rodino-Klapac.
Supervision: Straub, Mercuri, Ennamuri, Murphy, Manfrini, Elkins, Rodino-Klapac.

Conflict of Interest Disclosures: Dr Vandenborne reported receiving grants from Sarepta Therapeutics, Italfarmaco SPA, Astellas Pharma, Edgewise Therapeutics, Regenxbio, AskBio, Dyne Therapeutics, and the National Institutes of Health, all awarded to the University of Florida outside the submitted work. Dr Walter reported receiving funds for MR biomarker work from Sarepta Therapeutics to the University of Florida during the conduct of the study. Dr Straub reported receiving grants from Sarepta Therapeutics and advisory board/speaker honoraria from Pfizer outside the submitted work. Dr Willcocks reported receiving funding for data collection from Sarepta Therapeutics provided to the University of Florida during the conduct of the study. Dr Mercuri reported receiving advisory board/speaker fees from Sarepta Therapeutics outside the submitted work. Dr Muntoni reported receiving grants from Sarepta Therapeutics and Généthon and advisory board fees and/or symposia fees from Sarepta Therapeutics, Dyne Therapeutics, PTC Therapeutics, and Solid Bioscience outside the submitted work. Drs Ding, Ennamuri, and Elkins reported being employees of Sarepta Therapeutics Inc. Dr Reid reported owning stock options in F. Hoffmann-La Roche. Dr Murphy reported being employed by Roche Pharmaceuticals. Dr Mendell reported patients participating in the MRI study were treated at Nationwide Children's Hospital during the conduct of the study, receiving personal fees from Sarepta Therapeutics outside the submitted work, having a patent for AAV delivery of microdystrophin issued, and serving multiple roles in developing the product, treating the patients, and serving as a senior advisor for Sarepta Therapeutics (delandistrogene moxeparvovec was developed under Dr Mendell's supervision). Dr Rodino-Klapac reported receiving a patent for AAV delivery of muscle-specific micro-dystrophin to treat patients with muscular dystrophy licensed to Sarepta Therapeutics and being an employee of Sarepta Therapeutics. No other disclosures were reported.

Funding/Support: This study was sponsored by Sarepta Therapeutics Inc and funded by Sarepta Therapeutics Inc and F. Hoffmann-La Roche Ltd.

Role of the Funder/Sponsor: The sponsor had final responsibility for the design of the trial, protocol, database maintenance, trial conduct, data analyses and confirmation of the accuracy of the data.

Data Sharing Statement: See Supplement 4.

Additional Contributions: The authors thank the patients who participated in the EMBARK trial, their families, and caregivers; the staff who assisted with the trial and the principal investigators at the EMBARK study sites selected to perform MRI; Anne Connolly, MD (Nationwide Children's Hospital, Columbus, OH, USA), Carmen Leon Astudillo, MD (University of Florida Clinical Research Center, Gainesville, Florida), Susan Apkon, MD (Children's Hospital Colorado, Aurora, Colorado), Craig Zaidman, MD (St Louis Children's Hospital, St Louis, Missouri), Erika Finanger, MD (Oregon Health & Science University, Portland, Oregon), John Brandsema, MD (Children's Hospital of Philadelphia, Philadelphia, Pennsylvania), and Nicolas Deconinck, PhD (NMRC Gent [UZ Gent], Gent, Belgium). Medical writing and editorial assistance were provided by Leo Mahachi, PhD, and Jen Ciarochi, PhD, of Nucleus Global in accordance with Good Publication Practice 2022 guidelines and were funded by Sarepta Therapeutics Inc, Cambridge, Massachusetts, and F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Additional Information: Dr Mendell worked for Nationwide Children's Hospital in Ohio and The Ohio State University at the time of part 1 of the EMBARK trial.

REFERENCES

1. Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. *Nat Rev Dis Primers*. 2021;7(1):13. doi:10.1038/s41572-021-00248-3

2. Johnson EK, Zhang L, Adams ME, et al. Proteomic analysis reveals new cardiac-specific dystrophin-associated proteins. *PLoS One*. 2012;7(8):e43515. doi:10.1371/journal.pone.0043515

3. Pessina P, Cabrera D, Morales MG, et al. Novel and optimized strategies for inducing fibrosis in vivo: focus on Duchenne muscular dystrophy. *Skelet Muscle*. 2014;4:7. doi:10.1186/2044-5040-4-7

4. Lechner A, Herzig JJ, Kientsch JG, et al. Cardiomyopathy as cause of death in Duchenne muscular dystrophy: a longitudinal observational study. *ERJ Open Res*. 2023;9(5):00176-02023. doi:10.1183/23120541.00176-2023

5. Erkut E, Yokota T. CRISPR therapeutics for Duchenne muscular dystrophy. *Int J Mol Sci*. 2022;23(3):1832. doi:10.3390/ijms23031832

6. Sherlock SP, Palmer J, Wagner KR, et al. Quantitative magnetic resonance imaging measures as biomarkers of disease progression in boys with Duchenne muscular dystrophy: a phase 2 trial of domagrozumab. *J Neurol*. 2022;269(8):4421-4435. doi:10.1007/s00415-022-11084-0

7. Asher DR, Thapa K, Dharia SD, et al. Clinical development on the frontier: gene therapy for Duchenne muscular dystrophy. *Expert Opin Biol Ther*. 2020;20(3):263-274. doi:10.1080/14712598.2020.1725469

8. 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(9):1122-1131. doi:10.1001/jamaneurol.2020.1484

9. 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(1):332-341. doi:10.1038/s41591-024-03304-z

10. US Food and Drug Administration. ELEVIDYS(TM) Highlights of prescribing information. Accessed October 4, 2024. https://www.fda.gov/media/169679/download

11. UAE Ministry of Health & Prevention. Registered Medical Product Directory. Accessed October 4, 2024. https://mohap.gov.ae/en/registered-medical-product-directory

12. US Food and Drug Administration. FDA approves first gene therapy for treatment of certain patients with Duchenne muscular dystrophy. Accessed October 4, 2024. https://www.fda.gov/news-events/press-announcements/

fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy

13. Qatar Ministry of Public Health. Qatar National Formulary. Accessed October 4, 2024. https://www.moph.gov.qa/english/OurServices/advancedsearch/Pages/servicesdetails.aspx?serviceId=234

14. Kuwait Ministry of Health. Drug and dietary supplement price list. Accessed October 4, 2024. https://e.gov.kw/sites/kgoenglish/Pages/eServices/MOH/DrugFoodSupplementPrices.aspx

15. National Health Regulatory Authority Bahrain. Pharmacy & Pharmaceutical Products Regulation (PPR). Accessed October 4, 2024. https://www.nhra.bh/Departments/PPR/

16. Oman Ministry of Health. List of registered pharmaceutical manufacturers and products. Accessed October 4, 2024. https://www.moh.gov.om/en/hospitals-directorates/directorates-and-centers-at-hq/drug-safety-center/#Resources

17. Ministry of Health Israel. The Israeli Drug Registry. Accessed October 4, 2024. https://www.gov.il/en/service/israeli-drug-index

18. Potter RA, Griffin DA, Heller KN, et al. Dose-escalation study of systemically delivered rAAVrh74.MHCK7.micro-dystrophin in the mdx mouse model of Duchenne muscular dystrophy. *Hum Gene Ther*. 2021;32(7-8):375-389. doi:10.1089/hum.2019.255

19. A gene transfer therapy study to evaluate the safety and efficacy of SRP-9001 (delandistrogene moxeparvovec) in participants With Duchenne muscular dystrophy (DMD) (EMBARK). ClinicalTrials.gov identifier: NCT05096221. Updated December 10, 2024. Accessed October 4, 2024. https://clinicaltrials.gov/ct2/show//NCT05096221

20. Mendell JR, Sahenk Z, Lehman KJ, et al. Long-term safety and functional outcomes of delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy: a phase 1/2a nonrandomized trial. *Muscle Nerve*. 2024;69(1):93-98. doi:10.1002/mus.27955

21. Mendell JR, Shieh PB, McDonald CM, et al. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. *Front Cell Dev Biol*. 2023;11:1167762. doi:10.3389/fcell.2023.1167762

22. Zaidman CM, Proud CM, McDonald CM, et al. Delandistrogene moxeparvovec gene therapy in ambulatory patients (aged ≥4 to <8 years) with Duchenne muscular dystrophy: 1-year interim results from study SRP-9001-103 (ENDEAVOR). *Ann Neurol*. 2023;94(5):955-968. doi:10.1002/ana.26755

23. Schlaffke L, Rehmann R, Güttsches AK, et al. Evaluation of neuromuscular diseases and complaints by quantitative muscle MRI. *J Clin Med*. 2024;13(7):1958. doi:10.3390/jcm13071958

24. Willcocks RJ, Barnard AM, Daniels MJ, et al. Clinical importance of changes in magnetic resonance biomarkers for Duchenne muscular dystrophy. *Ann Clin Transl Neurol*. 2024;11(1):67-78. doi:10.1002/acn3.51933

25. Willcocks RJ, Forbes SC, Walter GA, et al. Assessment of rAAVrh.74.MHCK7.micro-dystrophin gene therapy using magnetic resonance imaging in children with Duchenne muscular dystrophy. *JAMA Netw Open*. 2021;4(1):e2031851. doi:10.1001/jamanetworkopen.2020.31851

26. Barnard AM, Willcocks RJ, Finanger EL, et al. Skeletal muscle magnetic resonance biomarkers correlate with function and sentinel events in Duchenne muscular dystrophy. *PLoS One*. 2018;13(3):e0194283. doi:10.1371/journal.pone.0194283

27. Rooney WD, Berlow YA, Triplett WT, et al. Modeling disease trajectory in Duchenne muscular dystrophy. *Neurology*. 2020;94(15):e1622-e1633. doi:10.1212/WNL.0000000000009244

28. Burakiewicz J, Sinclair CDJ, Fischer D, Walter GA, Kan HE, Hollingsworth KG. Quantifying fat replacement of muscle by quantitative MRI in muscular dystrophy. *J Neurol*. 2017;264(10):2053-2067. doi:10.1007/s00415-017-8547-3

29. Naarding KJ, Reyngoudt H, van Zwet EW, et al. MRI vastus lateralis fat fraction predicts loss of ambulation in Duchenne muscular dystrophy. *Neurology*. 2020;94(13):e1386-e1394. doi:10.1212/WNL.0000000000008939

30. Sanders M, Bowden AE, Baker S, Jensen R, Nichols M, Seeley MK. The influence of ambulatory aid on lower-extremity muscle activation during gait. *J Sport Rehabil*. 2018;27(3):230-236. doi:10.1123/jsr.2016-0148

31. Nöth U, Shrestha M, Schüre JR, Deichmann R. Quantitative in vivo T2 mapping using fast spin echo techniques—a linear correction procedure. *Neuroimage*. 2017;157:476-485. doi:10.1016/j.neuroimage.2017.06.017

32. Senesac CR, Barnard AM, Lott DJ, et al. Magnetic resonance imaging studies in Duchenne muscular dystrophy: linking findings to the physical therapy clinic. *Phys Ther*. 2020;100(11):2035-2048. doi:10.1093/ptj/pzaa140

33. Willcocks RJ, Arpan IA, Forbes SC, et al. Longitudinal measurements of MRI-T2 in boys with Duchenne muscular dystrophy: effects of age and disease progression. *Neuromuscul Disord*. 2014;24(5):393-401. doi:10.1016/j.nmd.2013.12.012

34. Willcocks RJ, Rooney WD, Triplett WT, et al. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large Duchenne muscular dystrophy cohort. *Ann Neurol*. 2016;79(4):535-547. doi:10.1002/ana.24599

35. Huang P, Goetz CG, Woolson RF, et al; Parkinson Study Group. Using global statistical tests in long-term Parkinson's disease clinical trials. *Mov Disord*. 2009;24(12):1732-1739. doi:10.1002/mds.22645

36. Schlaeger S, Sollmann N, Zoffl A, et al. Quantitative muscle MRI in patients with neuromuscular diseases-association of muscle proton density fat fraction with semi-quantitative grading of fatty infiltration and muscle strength at the thigh region. *Diagnostics (Basel)*. 2021;11(6):1056. doi:10.3390/diagnostics11061056

37. Sherlock SP, Zhang Y, Binks M, Marraffino S. Quantitative muscle MRI biomarkers in Duchenne muscular dystrophy: cross-sectional correlations with age and functional tests. *Biomark Med*. 2021;15(10):761-773. doi:10.2217/bmm-2020-0801

38. Liang Y, Li J, Yang C, et al. Muscle magnetic resonance imaging vs clinical function in Duchenne muscular dystrophy. *J Musculoskelet Disord Treat*. 2019;5(4):069. doi:10.23937/2572-3243.1510069

39. Barnard AM, Willcocks RJ, Triplett WT, et al. MR biomarkers predict clinical function in Duchenne muscular dystrophy. *Neurology*. 2020;94(9):e897-e909. doi:10.1212/WNL.0000000000009012

40. Arpan I, Willcocks RJ, Forbes SC, et al. Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. *Neurology*. 2014;83(11):974-980. doi:10.1212/WNL.0000000000000775

41. McDonald CM, Henricson EK, Abresch RT, et al; CINRG Investigators. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;391(10119):451-461. doi:10.1016/S0140-6736(17)32160-8

42. Zambon AA, Ayyar Gupta V, Ridout D, et al; UK Northstar Clinical Network. Peak functional ability and age at loss of ambulation in Duchenne muscular dystrophy. *Dev Med Child Neurol*. 2022;64(8):979-988. doi:10.1111/dmcn.15176