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Delandistrogene Moxeparvovec in Duchenne Muscular Dystrophy: Functional and Safety Outcomes up to 3 Years Post-Infusion in the EMBARK Study

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Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy that delivers a transgene encoding micro-dystrophin, an engineered, functional form of dystrophin shown to slow disease progression in ambulatory patients with DMD[1–4]
- Delandistrogene moxeparvovec is approved for the treatment of ambulatory patients with DMD in the USA and in other select countries[5,6]
- EMBARK (NCT05096221) is a Phase 3, multinational, double-blind, randomized, placebo-controlled, two-part study evaluating the safety and efficacy of delandistrogene moxeparvovec in ambulatory patients with DMD aged ≥4 to <8 years[7] (**Supplementary Figure 1**). While the primary endpoint of change from baseline in NSAA total score versus placebo was not met at Year 1, 2-year follow-up of Part 1-treated patients showed stabilization or slowing of DMD disease progression versus a matched EC cohort[1,2]
- Patients have now rolled over into the long-term follow-up EXPEDITION study (NCT05967351), an ongoing Phase 3 study which will follow approximately 400 patients from previous clinical trials for up to 5 years after delandistrogene moxeparvovec infusion[8]

Objectives

- We present 3-year functional efficacy and safety outcomes from patients treated with delandistrogene moxeparvovec in Part 1 of the EMBARK study (**Supplementary Table 1**), compared with a matched EC cohort

Methods

- In EMBARK Part 1 (1 year), patients received delandistrogene moxeparvovec (single IV dose, 1.33×10^{14} vg/kg) or placebo, with crossover to active treatment in Part 2 (1 year)
- In the absence of a placebo control after crossover, 3-year functional outcomes from patients treated in Part 1 of EMBARK were compared with a pre-defined matched EC cohort of patients with DMD using propensity-score weighting*
- Patients receiving only corticosteroid regimens from the FOR-DMD, BioMarin PRO-DMD-01, and CINRG DNHS studies were included[9–12]†
- Propensity-score weighting* was based on baseline:‡
  - Age, NSAA total score, TTR, 10MWR, height, weight, and BMI
- MMRM methods account for missing data. All *P*-values are nominal

*Inverse probability of treatment weighting. †Per medical judgement, stable frequency of corticosteroid use includes daily corticosteroid use and all non-daily steroid regimens which have been shown to have comparable functional outcomes to daily corticosteroid use. Daily, every other day, and two-day high dose regimens have been shown to have comparable functional outcomes. However, an intermittent regimen of 10 days on/10 days off was shown to be less efficacious compared with daily steroid use so these patients were excluded from the EC cohort.[2,13–15] As patients had rolled over into the long-term follow-up study, unknown potential confounders related to real-world treatment, including concomitant medications and differences in steroid regimens, are a limitation of this analysis. ‡Propensity-score weighting involves taking an EC group with similar age and function, but unequal distribution, and ensuring overlap after propensity-score weighting.

Results

- Baseline characteristics were matched between patients receiving delandistrogene moxeparvovec in EMBARK Part 1 (N=64) and EC patients (N=143) after propensity-score weighting (**Table 1**)

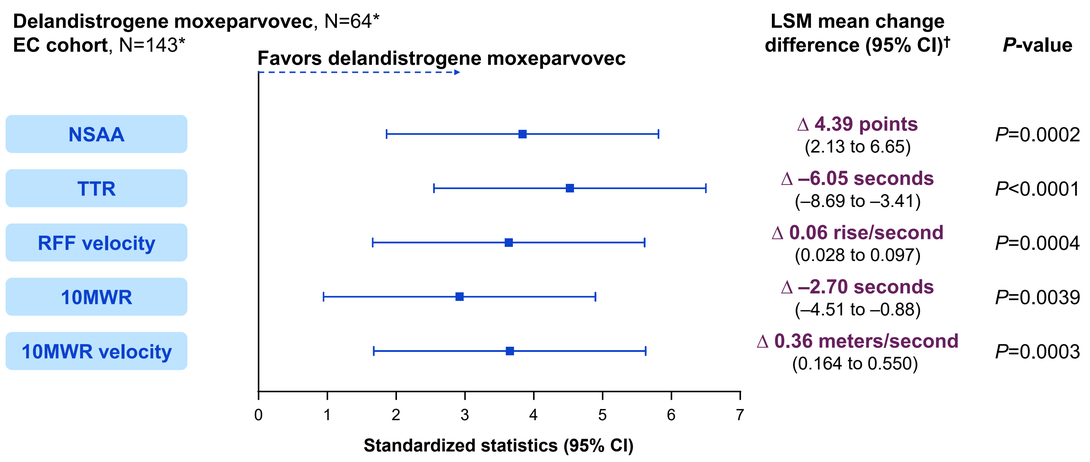
Table 1 *Demographics and baseline characteristics of patients receiving delandistrogene moxeparvovec in EMBARK Part 1 and the EC cohort*

Characteristic, Mean (min, max)	EMBARK Part 1 delandistrogene moxeparvovec (N=64)	EC cohort (N=143)	Standardized mean difference after propensity-score weighting*
Age, years	5.98 (4.07, 7.87)	6.24 (4.24, 7.99)	–0.281
NSAA total score, points	23.3 (14, 32)	23.5 (15, 32)	–0.045
TTR, time in seconds	3.51 (1.85, 5.75)	3.52 (1.90, 5.70)	–0.011
10MWR, time in seconds	4.80 (3.20, 6.85)	4.78 (3.00, 6.70)	0.034
Weight, kg	21.20 (13.5, 37.4)	22.18 (14.0, 36.0)	–0.198
Height, cm	108.65 (93.5, 127.0)	110.60 (94.9, 131.1)	–0.285
BMI, kg/m^2	17.80 (13.69, 24.92)	17.90 (13.74, 23.64)	–0.042

*Inverse probability of treatment weighting. A standardized mean difference of 0.25 (absolute value) is generally considered to indicate an adequate balance between the two groups.

- At 3 years post-infusion, clinically meaningful, durable, and nominally statistically significant functional benefits were observed across all key motor function measures for patients treated in Part 1 of EMBARK compared with the EC cohort (**Figure 1**)

Figure 1 *Functional outcomes of EMBARK Part 1-treated patients at 3 years compared with the EC cohort*



*All 64 patients treated with delandistrogene moxeparvovec and all 143 patients in the EC cohort were included in the analyses; MMRM methods account for missing data in these analyses. Twelve patients treated with delandistrogene moxeparvovec in Part 1 did not have 3-year follow-up data. In the EC cohort, 70 patients had missing Year 3 data for NSAA, 10MWR, and 10MWR velocity assessments, and 65 patients had missing Year 3 data for TTR and RFF velocity assessments. †LSMs (of change from baseline) and CIs were standardized in the forest plot by dividing by the SE. Negative values for timed function tests (TTR and 10MWR) show an improvement in the time taken to achieve these endpoints. LSM differences are on original scale (without SE adjustment). Signs of timed function tests were reversed in the forest plot to align favorable directions among endpoints. Numerical results of LSM difference kept the original signs. All *P*-values are nominal and have not been adjusted for multiple comparisons.

- Between Weeks 104 and 156, two (3.4%) patients experienced two TR-TEAEs (**Table 2**)
- No new safety signals were observed between Years 2 and 3; AEs typically begin within the first 90 days post-infusion[1,2]
- Between Years 2 and 3, there was a lower frequency of TR-TEAEs than during baseline to Year 2, and no TR-SAEs were reported

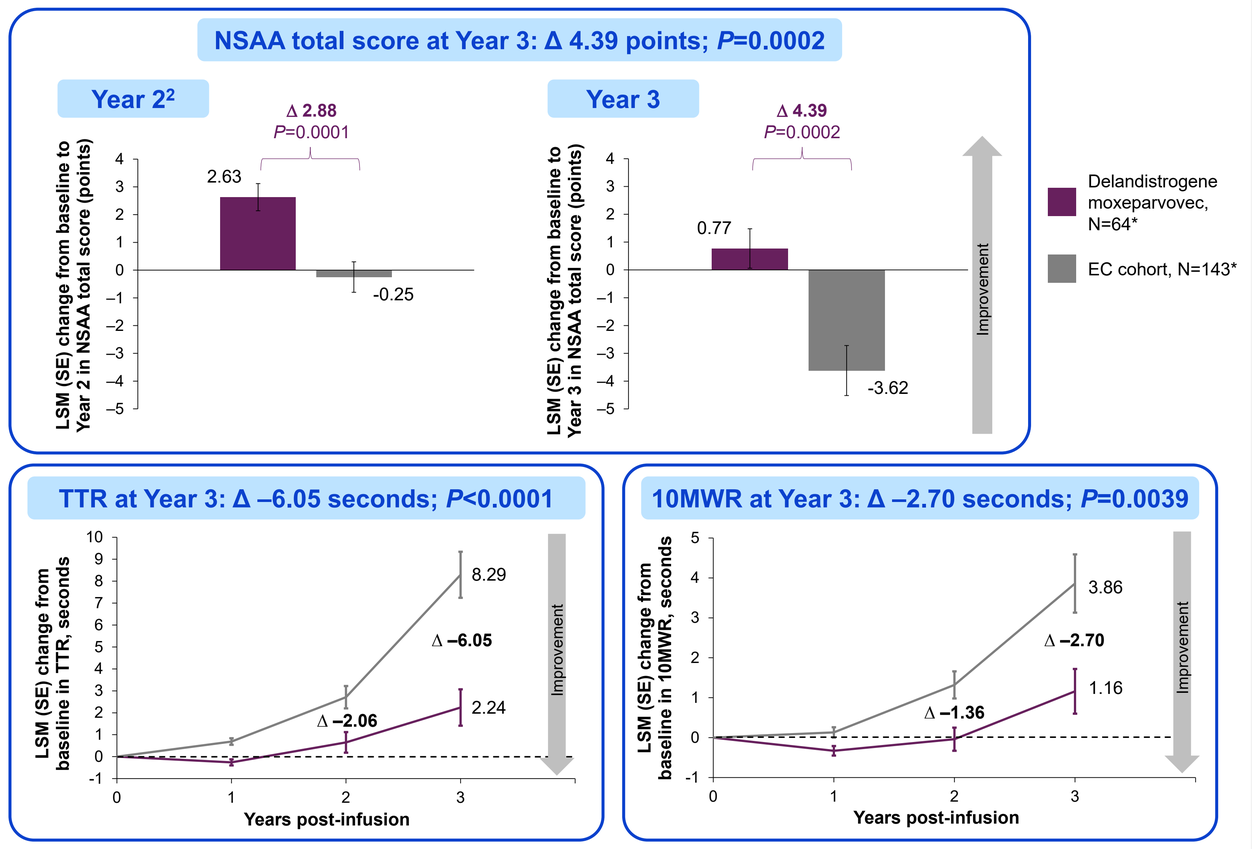
Table 2 *Overview of 3-year safety results in EMBARK Part 1-treated patients*

Overview of AEs, n (%)	Baseline to Year 1 N=63	Year 1 to Year 2* N=63	Year 2 to Year 3* N=58
Patients with any TEAEs	62 (98.4)	53 (84.1)	37 (63.8)
Patients with any SAEs	14 (22.2)	5 (7.9)	4 (6.9)
Patients with any TR-TEAEs	48 (76.2)	15 (23.8)	2 (3.4)
Number of TR-TEAEs	235	34	2†
Patients with any TR-SAEs	7 (11.1)	1 (1.6)	0 (0)
AEs leading to study discontinuation	0 (0)	0 (0)	0 (0)
Treatment-related deaths	0 (0)	0 (0)	0 (0)‡

*New events between Years 1 and 2 and Years 2 and 3, respectively (excludes ongoing events that began during the previous time period).
†Two TR-TEAEs of troponin-I increased. ‡One death assessed as unrelated to treatment was reported in a 9-year-old patient 931 days post-treatment.

- A widening treatment effect between Part 1 delandistrogene moxeparvovec-treated patients and the EC cohort was observed between 2 and 3 years post-infusion (**Figure 2**)[2]
- The majority of patients treated with delandistrogene moxeparvovec in EMBARK Part 1 remained above baseline in NSAA total score at 3 years post-infusion

Figure 2 *Change from baseline to Year 3 in functional outcomes of EMBARK Part 1-treated patients compared with the EC cohort*



*All 64 patients treated with delandistrogene moxeparvovec and all 143 patients in the EC cohort were included in the analyses; MMRM methods account for missing data in these analyses. Twelve patients treated with delandistrogene moxeparvovec in Part 1 did not have 3-year follow-up data. Two patients in EMBARK Part 1 lost ambulation between Year 2 and Year 3. In the EC cohort, 70 patients had missing Year 3 data for NSAA and 10MWR assessments, and 65 patients had missing Year 3 data for TTR assessments. All *P*-values are nominal and have not been adjusted for multiple comparisons.

- LVEF and LV fractional shortening do not indicate any cardiac safety signals over 3 years of follow-up (**Table 3**)

Table 3 *Cardiac data at 3 years in EMBARK Part 1-treated patients*

Mean (SD)	N	Baseline	Year 1	Year 2	Year 3
ECHO LVEF, %	50	65.3 (5.7)	65.2 (5.0)	64.5 (6.9)	60.5 (3.6)
ECHO LV fractional shortening, %	49	35.5 (4.5)	36.1 (6.4)	36.8 (8.2)	35.5 (3.6)

Conclusions

- At 3 years post-infusion (patients aged 7–10 years), patients treated with delandistrogene moxeparvovec in EMBARK Part 1 aged ≥4 to <8 years demonstrated clinically meaningful and durable functional benefits compared with a matched EC cohort
- Significant improvements were observed across all key motor function measures, with evidence of a widening treatment effect between Years 2 and 3, consistent with increasing divergence from natural history
- These findings demonstrate slowing of DMD progression, consistent with earlier observations of reduced muscle damage in treated patients as measured by MRI[3]
- No new safety signals were observed between Years 2 and 3, and the delandistrogene moxeparvovec safety profile remained consistent with prior experience and manageable with appropriate monitoring

Acknowledgments & Disclosures

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Disclosures: JRM received study funding from Sarepta Therapeutics, Inc. while at Nationwide Children's Hospital at the time of the study and is currently an employee of Sarepta Therapeutics, Inc. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology. FM has received honoraria and grants from Sarepta Therapeutics, Inc. for participating in symposia and advisory boards and is involved as an investigator in Sarepta Therapeutics, Inc. clinical trials. He reports participation in advisory boards for Novartis, F. Hoffmann-La Roche Ltd, Edgewise Therapeutics, Dyne Therapeutics, Pfizer, PTC Therapeutics, and Italfarmaco. CMM reports grants from Avidity, Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Solid Biosciences, and Sarepta Therapeutics, Inc., and has a consultancy/advisory role with Biomarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, NS Pharma, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, Solid Biosciences, and Sarepta Therapeutics, Inc. He has received honoraria from Edgewise Therapeutics, PTC Therapeutics, and Sarepta Therapeutics, Inc. EMM has received fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. EC has received honoraria from Sarepta Therapeutics, Inc. for participating in advisory boards and research and/or grant support from the Centers for Disease Control and Prevention, CureSMA, the Muscular Dystrophy Association, the National Institutes of Health, Orphazyme, the Patient-Centered Outcomes Research Institute, Parent Project Muscular Dystrophy, PTC Therapeutics, Santhera, Sarepta Therapeutics, Inc., and the US Food and Drug Administration. HK has received grants from Sarepta Therapeutics, Inc., Pfizer, PTC Therapeutics, Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Nippon Shinyaku Co., Ltd., and Kaneka Corporation. HK has received fees from Sarepta Therapeutics, Inc., Pfizer, PTC Therapeutics, Chugai Pharmaceutical Co., Nippon Shinyaku Co., and Kaneka Corporation. CL-A is an investigator in Sarepta Therapeutics, Inc. clinical trials and a sub-investigator in studies sponsored by Pfizer, Solid BioSciences, Edgewise Therapeutics, Italfarmaco, and Genentech/Roche. AN has received fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. CP participates in an advisory board and is a consultant for Biogen, Sarepta Therapeutics, Inc., AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; and is a principal investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO Pharma, Astellas, Biogen, CSL Behring, Fibrogen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, Inc., and Scholar Rock. US-S has received honoraria for counselling and participating in invited talks from Sarepta Therapeutics, Inc. and F. Hoffmann-La Roche Ltd. AV has a consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, Inc., UCB Pharma, Catalyst, and Scholar Rock; has received research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, the Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio, and Sarepta Therapeutics, Inc.; and has other relationship(s) with MedLink Neurology for editorial services. CMZ has received research support from Biogen and Novartis and has served on an advisory board for Sarepta Therapeutics, Inc. MF, JJ, MV, and DRA are employees of Sarepta Therapeutics, Inc. and may have stock options. APM, CR (at time of submission), and COT are employees of Roche Products Ltd and may have stock options in F. Hoffmann-La Roche Ltd. MG and MM are employees of F. Hoffmann-La Roche Ltd and may have stock options. LRR-K is an employee of Sarepta Therapeutics, Inc. and may have stock options. In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

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Abbreviations

10MWR, 10-meter Walk/Run; AE, adverse event; BMI, body mass index; CI, confidence interval; DMD, Duchenne muscular dystrophy; EC, external control; ECHO, echocardiogram; IV, intravenous; LSM, least-squares mean; LV, left ventricular; LVEF, left ventricular ejection fraction; MMRM, mixed effects model for repeated measures; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; RFF, rise from floor; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise; vg/kg, vector genomes per kilogram.

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1. Mendell JR, et al. *Nat Med*. 2025; 31:332–341; **2.** Mendell JR, et al. *Neurol Ther*. 2026; doi:10.1007/s40120-025-00879-8 (Online ahead of print); **3.** Vandenborne K, et al. *JAMA Neurol*. 2025; 82:734–744; **4.** Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131; **5.** US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information. https://www.fda.gov/media/169679/download (Accessed March 2026); **6.** Jolly H, et al. *Lancet*. 2025; 3;405:1572–1573; **7.** ClinicalTrials.gov. NCT05096221 (Accessed March 2026); **8.** ClinicalTrials.gov. NCT05967351 (Accessed March 2026); **9.** ClinicalTrials.gov. NCT01603407 (Accessed March 2026); **10.** ClinicalTrials.gov. NCT01753804 (Accessed March 2026); **11.** ClinicalTrials.gov. NCT00468832 (Accessed March 2026); **12.** Spurney C, et al. *Muscle Nerve*. 2014; 50:250–256; **13.** Escolar DM, et al. *Neurology*. 2011; 77:444–452; **14.** Fenichel GM, et al. *Arch Neurol*. 1991; 48:575–579; **15.** Guglieri M, et al. *JAMA*. 2022; 327:1456–1468.

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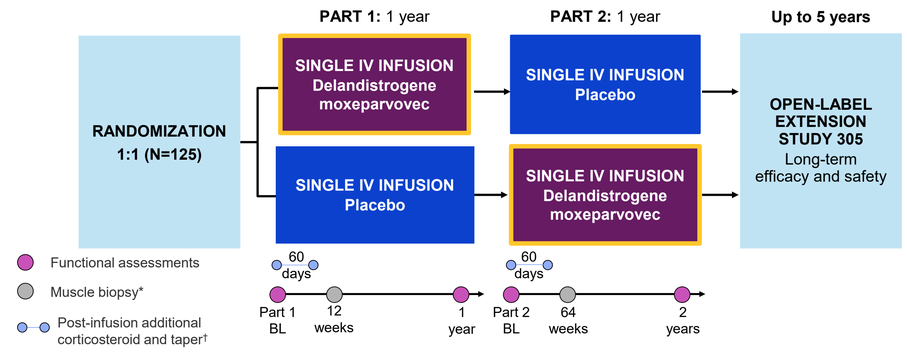
Supplementary information

Supplementary Figure 1 *EMBARK study design*[1]



*Only a subset of patients received a muscle biopsy for expression assessments, based on site experience and feasibility. †Starting the day before infusion, patients received additional corticosteroids (prednisone 1 mg/kg/day) in addition to their baseline stable corticosteroid dose. On Day 60, the additional corticosteroid dose was tapered over a 2-week period, after which patients continued their baseline stable dose for the remainder of the study.

Supplementary Table 1 *Key inclusion criteria*[1]

Key inclusion criteria	
Ambulatory males aged ≥4 to <8 years at randomization	TTR <5 seconds at screening
Confirmed DMD diagnosis (*DMD* mutation fully contained within exons 18–79 [inclusive], excluding mutations fully contained within exon 45 [inclusive])	On a stable daily dose of oral corticosteroids for ≥12 weeks before screening
Ability to cooperate with motor assessment testing	rAAVrh74 total binding antibody titers <1:400
NSAA total score >16 and <29 points at screening	

Abbreviations

BL, baseline; DMD, Duchenne muscular dystrophy; IV, intravenous; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; TTR, Time to Rise.

Reference

1. ClinicalTrials.gov. NCT05096221 (Accessed March 2026).