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Long-Term Functional Outcomes, Safety, and Micro-Dystrophin Expression Following Delandistrogene Moxeparvovec Treatment in DMD: EMBARK 2-Year Results

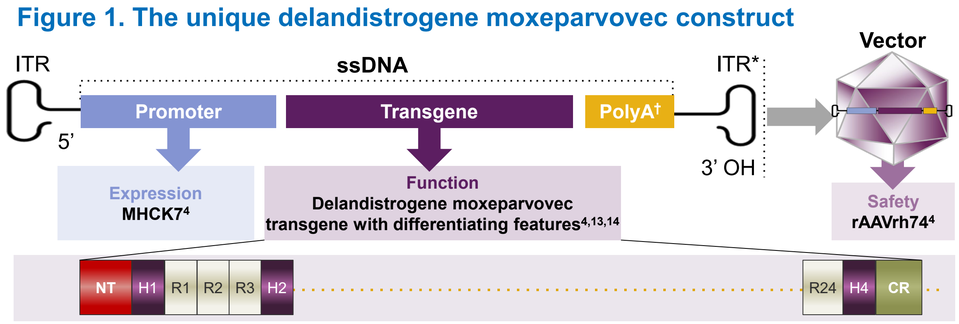
Jerry R. Mendell,[1] Francesco Muntoni,[2] Craig M. McDonald,[3] Eugenio M. Mercuri,[4] Emma Ciafaloni,[5] Hirofumi Komaki,[6] Carmen Leon-Astudillo,[7] Andrés Nascimento,[8] Crystal Proud,[9] Ulrike Schara-Schmidt,[10] Aravindhan Veerapandiyan,[11] Craig M. Zaidman,[12] Matthew Furgerson,[1] Kai Ding,[1] Preeti Singh,[1] Rachael Potter,[1] Damon R. Asher,[1] Alexander P. Murphy,[13] Carol Reid,[13] Gregory Hooper,[13] Carmen O. Torre,[13] Marianna Manfrini,[14] Jacob S. Elkins,[1] Louise R. Rodino-Klapac,[1] on behalf of the EMBARK Study Group

[1]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]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, UK; [3]UC Davis Health, Sacramento, CA, USA; [4]Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [5]University of Rochester Medical Center, Rochester, NY, USA; [6]Translational Medical Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan; [7]Department of Pediatrics, University of Florida, Gainesville, FL, USA; [8]Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu, CIBERER – ISC III, Barcelona, Spain; [9]Children's Hospital of the King's Daughters, Norfolk, VA, USA; [10]Department of Pediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Essen, University of Duisburg-Essen, Essen, Germany; [11]Department of Pediatrics, Division of Neurology, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR, USA; [12]Department of Neurology, Washington University in St Louis, St Louis, MO, USA; [13]Roche Products Ltd, Welwyn Garden City, UK; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered, functional form of dystrophin shown to stabilize or slow disease progression in DMD (**Figure 1**)[1–4]
- Delandistrogene moxeparvovec is approved in the USA and in other select countries[5–12]

Figure 1. The unique delandistrogene moxeparvovec construct



*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes it.

Objective

- We present 2-year functional outcomes from patients treated with delandistrogene moxeparvovec in Part 1 of EMBARK compared with a well-matched external control (EC) cohort. Week 64 delandistrogene moxeparvovec micro-dystrophin expression and sarcolemmal localization and 2-year safety outcomes are also reported

Methods

- In the absence of a placebo arm, due to the crossover study design (**Supplementary Figure 1**), 2-year data of EMBARK Part 1-treated patients were compared with an EC cohort of patients with DMD using propensity-score weighting[15–17]*
- Patients receiving only corticosteroid regimens from the FOR-DMD, BioMarin PRO-DMD-01, and CINRG DNHS studies were included[18–21]

External control (EC) cohort entry criteria

- Aged ≥4 and <8 years
- NSAA total score ≥14 and ≤32
- TTR ≤5.75 seconds
- 10MWR time ≤6.85 seconds
- Stable dose of oral corticosteroids for ≥12 weeks
- Had both baseline and at least 1 post-baseline assessment values

Propensity-score weighting* was based on baseline:†

- Age
- NSAA total score
- TTR
- 10MWR
- Height
- Weight
- BMI

*Inverse probability of treatment weighting. †Propensity-score weighting involves taking an EC group with similar age and function, but unequal distribution, and ensuring overlap after propensity-score weighting.

Results

- Prior to propensity-score weighting, there were 155 patients in the EC cohort who met the entry criteria and had at least 1 post-baseline visit (FOR-DMD, n=89; BioMarin PRO-DMD-01, n=41; CINRG DNHS, n=25)
- Baseline characteristics were well matched between patients receiving delandistrogene moxeparvovec in EMBARK Part 1 and EC patients 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/m²	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.

- Mean delandistrogene moxeparvovec micro-dystrophin expression and sarcolemmal localization were sustained from Week 12 to Week 64 in a subset of patients (**Table 2**)

Table 2. Delandistrogene moxeparvovec micro-dystrophin expression and sarcolemmal localization at Week 12 and Week 64

Mean (SD)	Week 12, n=17	Week 64, n=16
Western blot, % control	34.29 (41.04)	45.68 (39.75)
PDPF, %	28.13 (26.10)	38.60 (26.93)

- Between Weeks 52 and 104, 15 (23.8%) patients experienced 34 TR-TEAEs (**Table 3**)
- One patient experienced two TR-SAEs of rhabdomyolysis; both resolved
- There were no treatment-related AEs leading to death or discontinuation and there were no clinically significant complement-mediated AEs
- Evidence to date suggests that most TR-TEAEs were reported within the first 90 days (**Figure 4**)

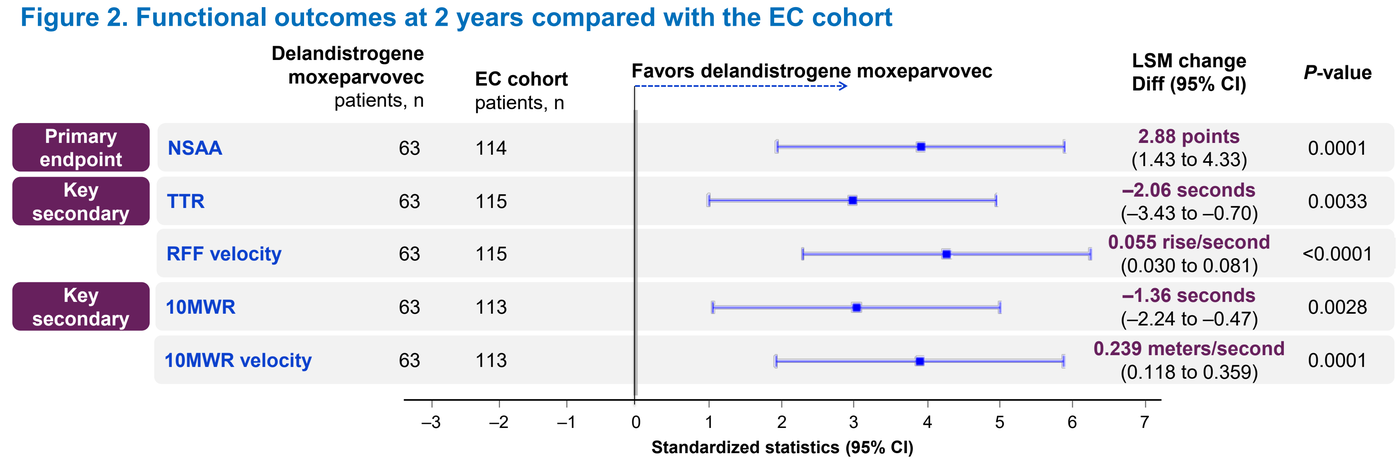
Table 3. Delandistrogene moxeparvovec safety overview

Overview of AEs, n (%)	Baseline to Week 52, N=63	Weeks 52–104,* N=63
Patients with any TEAEs	62 (98.4)	53 (84.1)
Patients with any SAEs	14 (22.2)	5 (7.9)
Patients with any TR-TEAEs	48 (76.2)	15 (23.8)
Number of TR-TEAEs	235	34
Patients with any TR-SAEs	7 (11.1)	1 (1.6)
AEs leading to study discontinuation	0 (0)	0 (0)
Deaths	0 (0)	0 (0)

*New events between Weeks 52 and 104 (excludes ongoing events that began during Part 1 of EMBARK [baseline to Week 52]). †TR-TEAEs occurring in >10% of patients in EMBARK Part 1 or in >3% of patients in Part 2. ‡GLDH increases were based on investigator assessment and their institution's normal range.

- At 2 years, EMBARK Part 1 delandistrogene moxeparvovec-treated patients demonstrated statistically significant and clinically meaningful functional benefit in NSAA total score, TTR, RFF velocity, 10MWR, and 10MWR velocity versus a propensity-score-weighted EC cohort (**Figures 2 and 3**)
- Other secondary endpoints were stable at Year 2 (**Supplementary Figure 2**)

Figure 2. Functional outcomes at 2 years compared with the EC cohort



LSMs (of change from baseline) and CIs were standardized 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 reported are nominal and have not been adjusted for multiple comparisons.

Figure 3. Change from baseline to Year 2 in functional outcomes

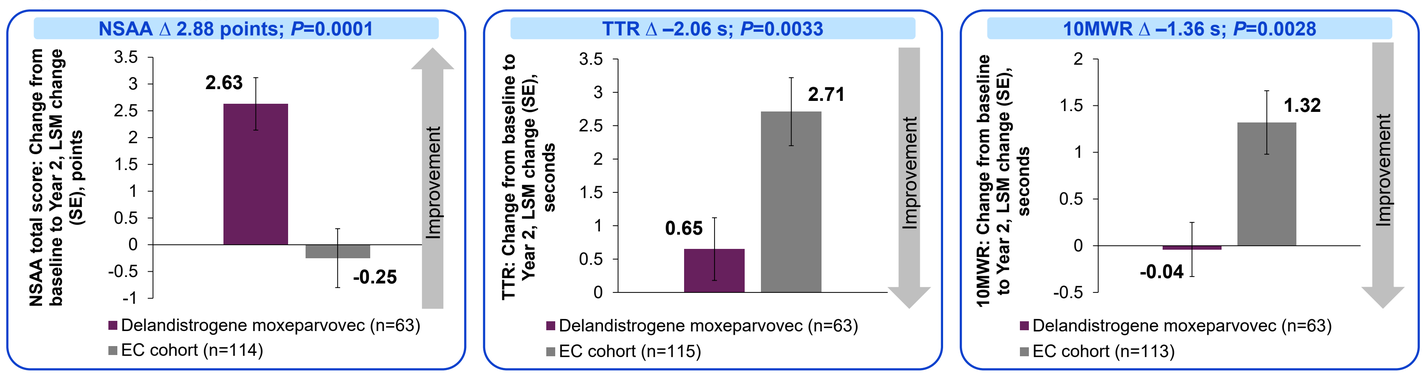


Figure 4. Number of patients with TR-TEAEs, listed by frequency at 0–2 weeks, n (%)†

	0–2 weeks	>2 weeks to 60 days	>60 days to 12 weeks	>12 weeks to Week 52	Week 52 to Week 104
Vomiting	31 (49.2)	3 (4.8)	0 (0)	0 (0)	0 (0)
Nausea	19 (30.2)	1 (1.6)	0 (0)	0 (0)	1 (1.6)
Decreased appetite	16 (25.4)	1 (1.6)	0 (0)	0 (0)	0 (0)
Pyrexia	10 (15.9)	0 (0)	0 (0)	0 (0)	1 (1.6)
Abdominal pain upper	7 (11.1)	1 (1.6)	0 (0)	0 (0)	0 (0)
GLDH increased‡	3 (4.8)	11 (17.5)	1 (1.6)	1 (1.6)	0 (0)
Headache	2 (3.2)	0 (0)	0 (0)	0 (0)	2 (3.2)
Gamma-glutamyl transferase increase	0 (0)	5 (7.9)	0 (0)	0 (0)	1 (1.6)
Troponin-I increase	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.3)
Proteinuria	0 (0)	0 (0)	0 (0)	1 (1.6)	2 (3.2)
Day 1 infusion					

Conclusions

- Two-year results from EMBARK demonstrate statistically significant and clinically meaningful differences between the treatment group and well-matched EC cohort in functional outcomes prognostic for delaying loss of ambulation, indicating stabilization or slowing of disease progression
- Sustained micro-dystrophin expression and localization to the sarcolemma up to Week 64 demonstrate durability of the delandistrogene moxeparvovec treatment effect
- Two-year safety outcomes of EMBARK Part 1-treated patients were consistent with prior experience from the delandistrogene moxeparvovec clinical development program

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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; GLDH, glutamate dehydrogenase; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; NT, N-terminal; PDPF, percent dystrophin-positive fibers; 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-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise.

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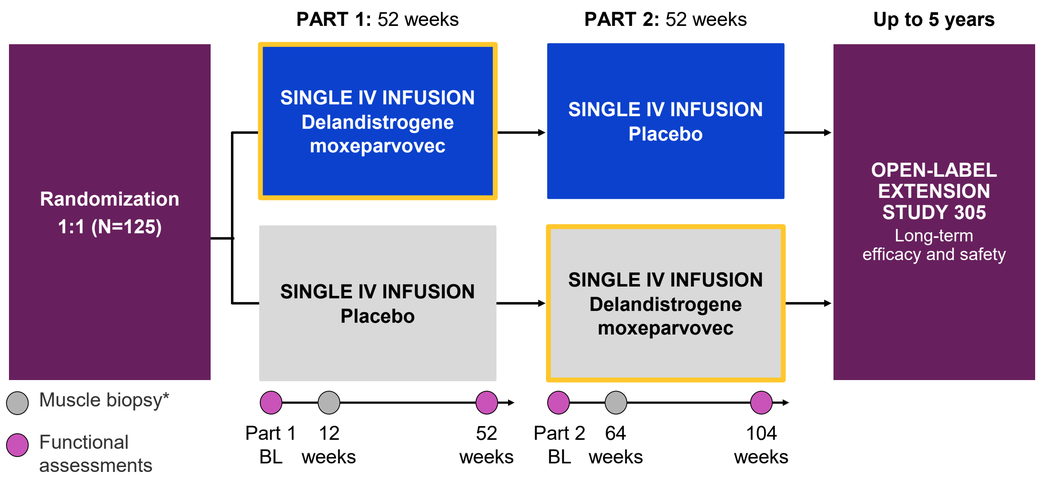
Supplementary Information

Supplementary Figure 1. EMBARK study design[1,2]

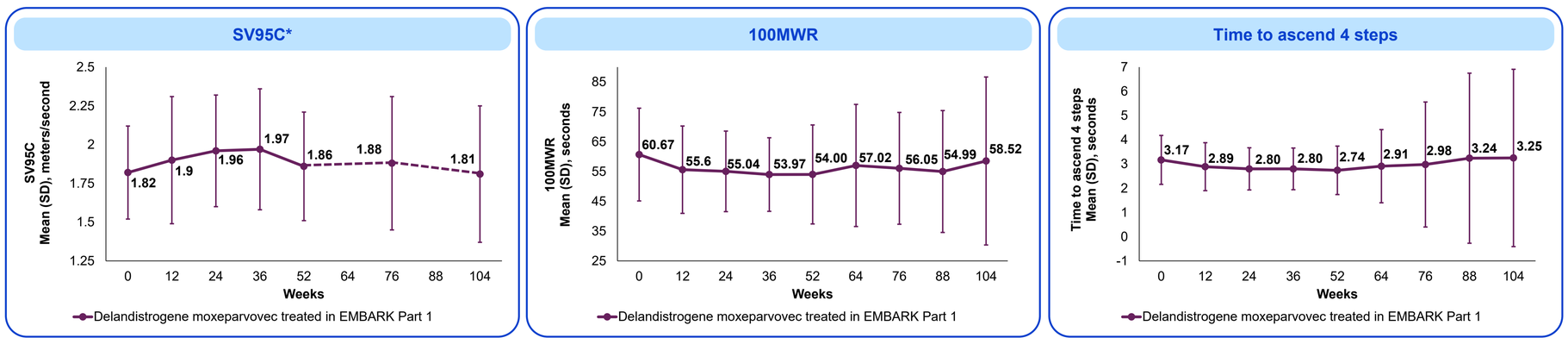


Key inclusion criteria

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

*Only a subset of patients receive a muscle biopsy for expression assessments, based on site experience and feasibility.

Supplementary Figure 2. Additional functional outcomes over 2-years



*Data are not available for Weeks 64 and 88.

Abbreviations

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

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1. ClinicalTrials.gov. NCT05096221 (Accessed March 2025);
2. Mendell JR, et al. *Nat Med*. 2025; 31:332–341.