

3-Year Functional Outcomes of Patients With Duchenne Muscular Dystrophy: Pooled Delandistrogene Moxeparovec Clinical Trial Data vs External Controls

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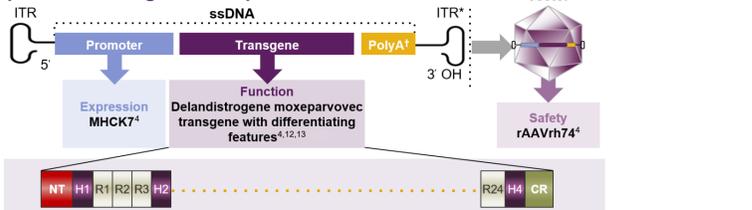
OBJECTIVE

- To compare 3-year functional outcomes of ambulatory patients treated in delandistrogene moxeparovec clinical trials with those of propensity-score-weighted ECs to contextualize long-term treatment effects

BACKGROUND

- Delandistrogene moxeparovec is an rAAVrh74 vector-based gene transfer therapy for DMD with high affinity for skeletal, respiratory, and cardiac muscles¹⁻⁴ (Figure 1)
- It delivers a transgene encoding delandistrogene moxeparovec micro-dystrophin¹⁻⁴ which is approved in the US and other select countries⁵⁻¹¹
- We previously compared 1-year functional data from patients with DMD who participated in delandistrogene moxeparovec clinical trials with data from a cohort of well-matched EC patients that suggested a beneficial modification of the DMD disease trajectory in the patients who received treatment⁵

Figure 1. The unique delandistrogene moxeparovec construct



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

METHODS

Analysis set

- Functional outcomes data were pooled from 50 patients with DMD enrolled in 3 studies (Figure 2)

Figure 2. Sources of clinical trial data

Study	Description	Delandistrogene moxeparovec (n=50)
Study 101 (NCT03375164, n=4) ⁶	Phase 1/2 study of delandistrogene moxeparovec in ambulatory patients with DMD	Entry criteria • Target dose: 1.33×10^{14} vg/kg • Age at dosing: ≥ 4 to < 9 years • Had both a baseline value and a year 3 post-baseline value
Study 102 (NCT03769116, n=26) ⁷	Phase 2 study of delandistrogene moxeparovec in ambulatory patients with DMD	
ENDEAVOR Cohort 1 (NCT04626674, n=20) ⁸	Phase 1b study of delandistrogene moxeparovec in ambulatory patients with DMD	

- EC cohort, before PSW, included 83 patients with DMD pooled from 3 natural history and clinical trial studies (Figure 3)

Figure 3. Sources of external control data

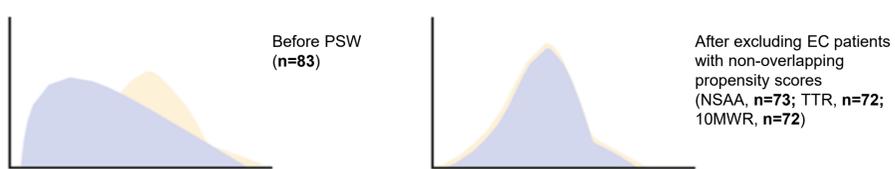
Study	Description	EC (n=83)
FOR-DMD (NCT01603407, n=68) ^{9,*}	Phase 3 randomized trial in ambulatory patients with DMD on corticosteroid regimens	Entry criteria • Age at baseline: ≥ 4 to < 9 years • NSAA total score: ≥ 13 and ≤ 30 points • RFF time: ≤ 10.4 s • 10MWR time: ≤ 9.1 s • Stable corticosteroid dose: ≥ 12 weeks • Had both a baseline value and a year 3 post-baseline value
BioMarin PRO-DMD-01 (NCT01753804, n=12) ^{10,*}	Prospective natural history study in ambulatory/non-ambulatory patients with DMD	
CINRG DNHS (NCT00468832, n=3) ^{11,*}	Prospective natural history study	

*Only the patients who were receiving a stable corticosteroid regimen were included in the EC cohort. †May also be referred to as TTR.

Statistical analyses

- PSW was performed to ensure maximum comparability between the EC cohort and the delandistrogene moxeparovec groups based on the following baseline parameters (Figure 4):
 - Age
 - Height
 - NSAA total score
 - Weight
 - RFF
 - BMI
 - 10MWR
- Following PSW, median regression and MMRM analyses were conducted for each of the following functional endpoints comparing delandistrogene moxeparovec and EC cohorts:
 - CFBL at year 3 in NSAA total score
 - CFBL at year 3 in RFF (velocity and time)
 - CFBL at year 3 in 10MWR (velocity and time)
- MMRM was the primary analysis; median regression (shown here, because of the non-normal data distribution) was the sensitivity analysis

Figure 4. External controls cohort before and after PSW*



*PSW involves taking an EC group with similar age and function, but unequal distribution, and ensuring overlap after PSW.

RESULTS

- Pooled treatment group and EC cohort had similar baseline covariate values after PSW (Table 1)

Table 1. Baseline covariates before and after propensity-score weighting (3-year total analysis sets)

		Delandistrogene moxeparovec (n=50)	EC cohort before PSW (n=83)	EC cohort after PSW (n=73)	Standardized mean difference, treatment vs EC after PSW
Age, years	Mean (SD)	6.4 (1.30)	6.5 (1.0)	6.5 (0.74)	-0.14
	Median (range)	6.3 (4.0-8.9)	6.5 (4.8-8.9)	6.5 (4.8-8.9)	
NSAA total score, points	Mean (SD)	22.3 (3.7)	23.9 (4.4)	21.7 (4.0)	0.15
	Median (range)	22 (13-30)	24 (13-30)	21 (13-30)	
RFF time, s	Mean (SD)	4.4 (1.8)	4.5 (1.6)	4.4 (1.2)	-0.05
	Median (range)	3.9 (2.4-10.4)	4.3 (2.0-10.2)	4.2 (2.0-10.2)	
10MWR time, s	Mean (SD)	5.1 (1.1)	5.3 (1.0)	5.1 (0.8)	-0.04
	Median (range)	4.9 (3.5-9.1)	5.2 (3.6-7.9)	5.1 (3.6-7.9)	
Weight, kg	Mean (SD)	22.7 (4.7)	21.3 (4.8)	23.3 (4.0)	-0.13
	Median (range)	22.0 (13.7-34.5)	20.3 (14.0-39.0)	22.6 (15.9-35.9)	
Height, cm	Mean (SD)	111.8 (7.7)	111.9 (7.6)	112.9 (5.2)	-0.14
	Median (range)	113.1 (94.4-124.0)	111.3 (99.0-142.0)	113.0 (99.0-130.2)	
BMI, kg/m ²	Mean (SD)	18.1 (2.4)	16.8 (2.1)	18.2 (2.1)	-0.06
	Median (range)	17.5 (13.2-24.6)	16.4 (13.7-22.5)	17.5 (13.7-22.5)	

Both MMRM (primary analysis; use QR code to access Appendix) and median regression (sensitivity analysis) showed long-term stabilization or slowing of disease progression at 3 years in the pooled treatment group vs the EC cohort, as measured via NSAA total score (Figure 5), RFF time and velocity (Figure 6), and 10MWR time and velocity (Figure 7)

Figure 5. 3-year median change from baseline in NSAA total score

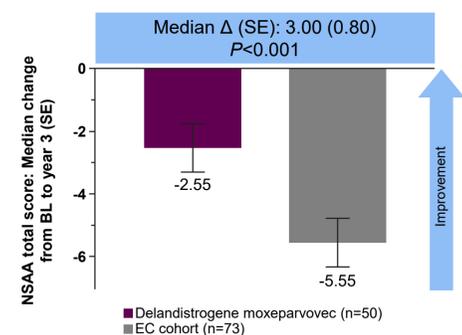


Figure 6. 3-year median change from baseline in RFF time and velocity

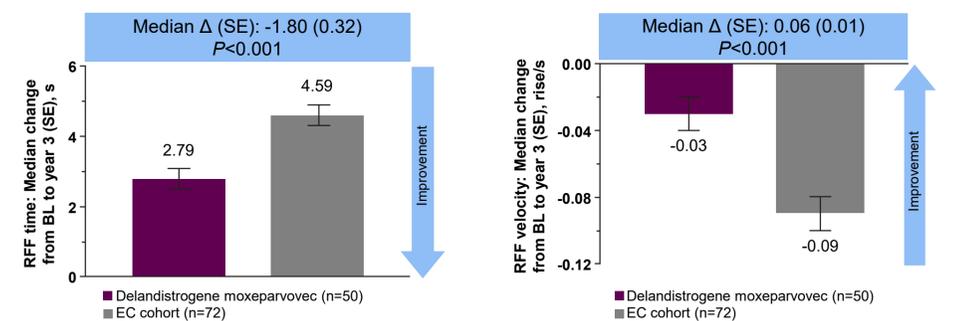
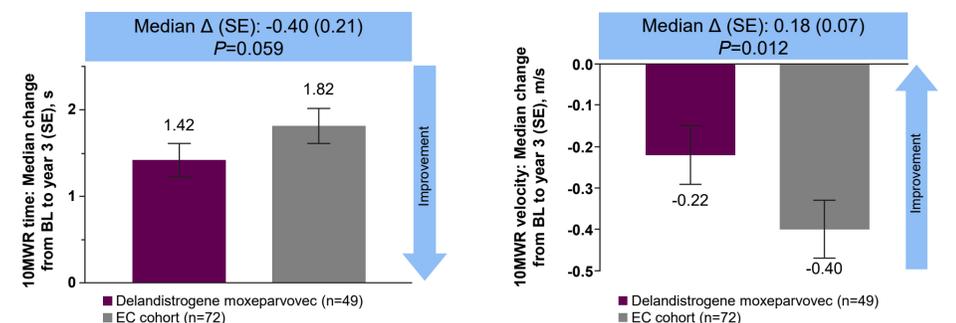


Figure 7. 3-year median changes from baseline in 10MWR time and velocity



Conclusions

- At 3 years, patients treated with delandistrogene moxeparovec demonstrated long-term stabilization or slowing of disease progression compared with a well-matched EC cohort, as measured via NSAA total score, RFF time and velocity, and 10MWR time and velocity, and analyzed using MMRM and median regression
- These data suggest that delandistrogene moxeparovec has a clinically meaningful long-term impact on the disease course of DMD, modifying its trajectory relative to the natural history of the disease

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Abbreviations

10MWR, 10-meter walk/run; BL, baseline; BMI, body mass index; CFBL, changes from baseline; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; DNHS, Duchenne Natural History Study; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; ITR, inverted terminal repeat; LSM, least-squares mean; MMRM, mixed-effects model for repeated measures; NSAA, North Star Ambulatory Assessment; NT, N-terminal; polyA, polyadenylation; PSW, propensity-score weighting; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; RFF, rise from floor; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TTR, time to rise; vg, vector genome.

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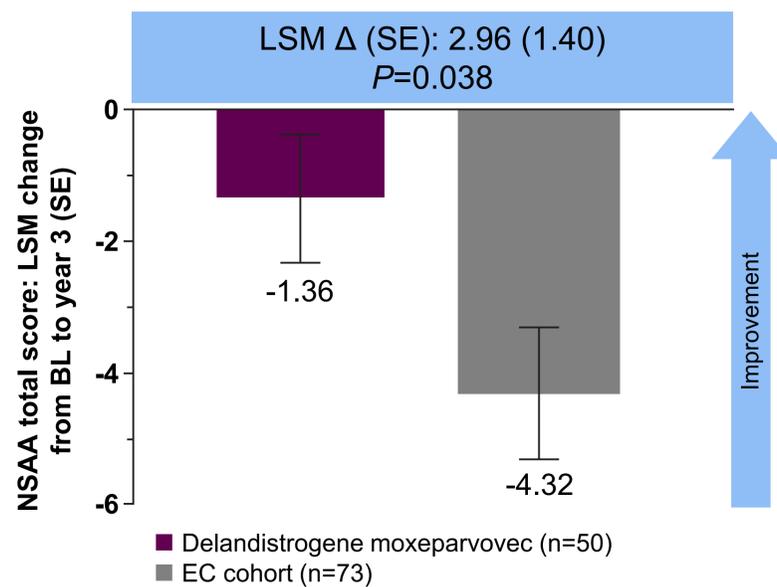
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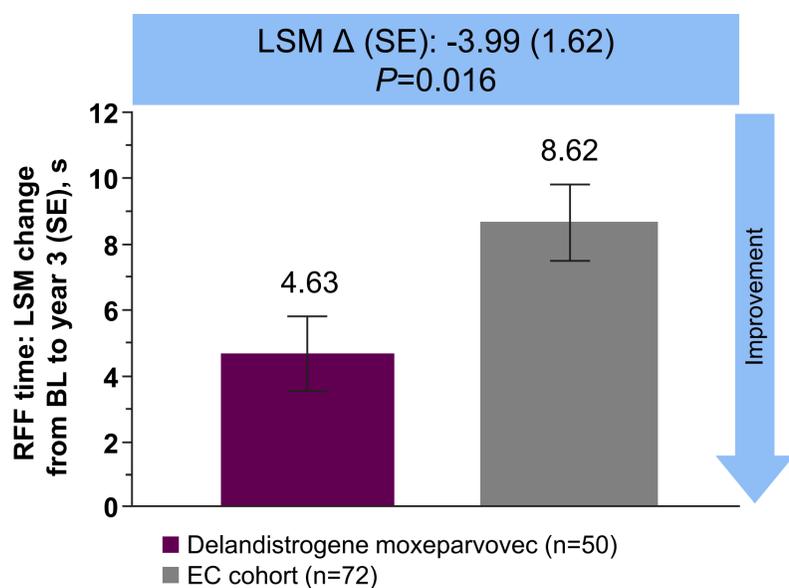
SUPPLEMENTARY INFORMATION

Appendix: Changes in NSAA Total Score, RFF Time and Velocity, and 10MWR Time and Velocity (MMRM)

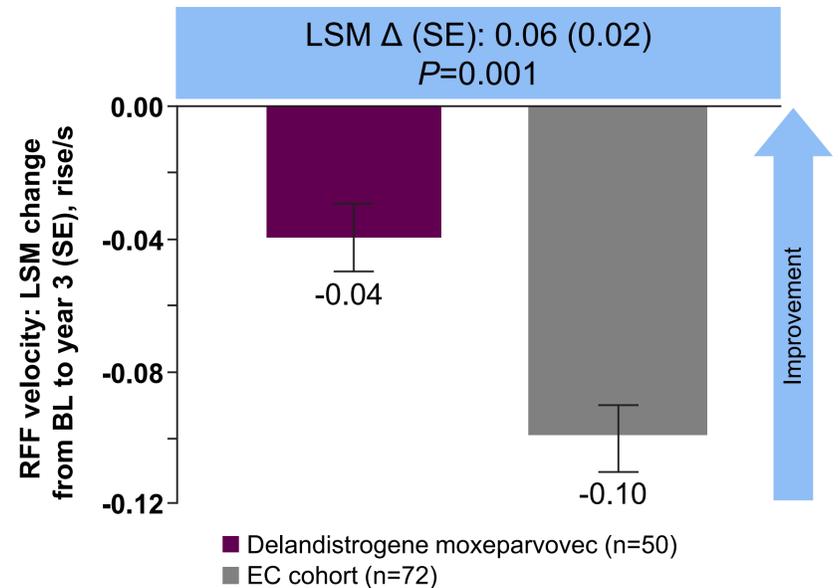
NSAA Total Score



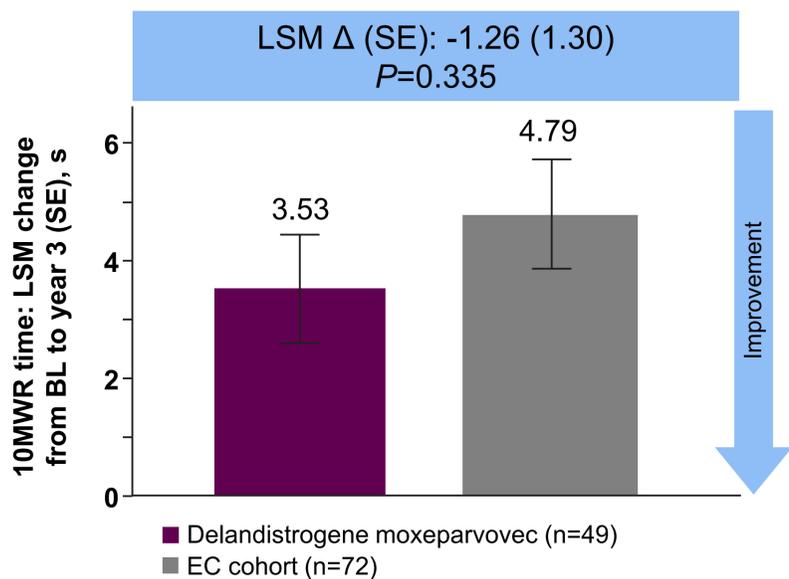
RFF Time



RFF Velocity



10MWR Time



10MWR Velocity

