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

Jerry R. Mendell[1]; Anne M. Connolly[2]; John Day[3]; Craig M. McDonald[4]; Crystal M. Proud[5]; Perry Shieh[6]; Craig M. Zaidman[7]; Matthew Furgerson[1]; Kai Ding[1]; Carol Reid[8]; Alexander P. Murphy[8]; Louise R. Rodino-Klapac[1]

[1]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]Chief of Neurology Division, Nationwide Children's Hospital, Columbus, OH, USA, and Professor of Pediatrics at The Ohio State University College of Medicine, Columbus, OH, USA; [3]Professor, of Neurology and Neurological Sciences (Adult Neurology), of Pediatrics (Genetics) and, by courtesy, of Pathology, Stanford University, Palo Alto, CA, USA; [4]Chair, Department of Physical Medicine & Rehabilitation and Professor, Departments of Pediatrics and Physical Medicine & Rehabilitation, UC Davis, Davis, CA, USA; [5]Pediatric Neurologist and Director of Neurology, Children's Hospital of The King's Daughters, Norfolk, VA, USA; [6]Neurologist, UCLA Health, Los Angeles, CA, USA; [7]Professor of Neurology and of Pediatrics, Washington University in St. Louis, St. Louis, MO, USA; [8]Roche Products Ltd, Welwyn Garden City, UK
Corresponding email address: medinfo@sarepta.com

OBJECTIVE

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

BACKGROUND

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy for DMD with high affinity for skeletal, respiratory, and cardiac muscles[1-4] (Figure 1)
- It delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin,[1-4] which is approved in the US and other select countries[5-11]
- We previously compared 1-year functional data from patients with DMD who participated in delandistrogene moxeparvovec 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 treatment[5]

Figure 1. The unique delandistrogene moxeparvovec construct
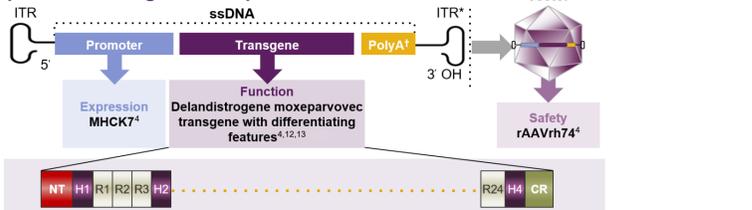
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (ie, copies) it.

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

- EC cohort, before PSW, included 83 patients with DMD pooled from 3 natural history and clinical trial studies (Figure 3)
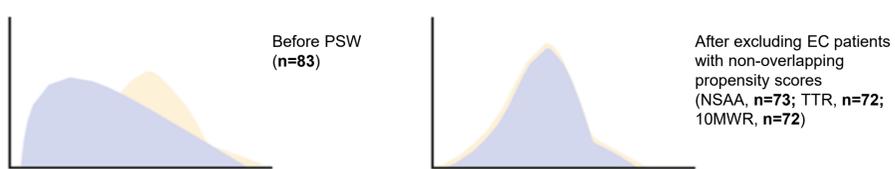
Figure 3. Sources of external control data

*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 moxeparvovec groups based on the following baseline parameters (Figure 4):
  - Age
  - NSAA total score
  - RFF
  - 10MWR
  - Height
  - Weight
  - BMI
- Following PSW, median regression and MMRM analyses were conducted for each of the following functional endpoints comparing delandistrogene moxeparvovec 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*

Before PSW (n=83)

After excluding EC patients with non-overlapping propensity scores (NSAA, n=73; TTR, n=72; 10MWR, n=72)

*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 moxeparvovec (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) Median (range)	6.4 (1.30) 6.3 (4.0-8.9)	6.5 (1.0) 6.5 (4.8-8.9)	6.5 (0.74) 6.5 (4.8-8.9)	-0.14
NSAA total score, points	Mean (SD) Median (range)	22.3 (3.7) 22 (13-30)	23.9 (4.4) 24 (13-30)	21.7 (4.0) 21 (13-30)	0.15
RFF time, s	Mean (SD) Median (range)	4.4 (1.8) 3.9 (2.4-10.4)	4.5 (1.6) 4.3 (2.0-10.2)	4.4 (1.2) 4.2 (2.0-10.2)	-0.05
10MWR time, s	Mean (SD) Median (range)	5.1 (1.1) 4.9 (3.5-9.1)	5.3 (1.0) 5.2 (3.6-7.9)	5.1 (0.8) 5.1 (3.6-7.9)	-0.04
Weight, kg	Mean (SD) Median (range)	22.7 (4.7) 22.0 (13.7-34.5)	21.3 (4.8) 20.3 (14.0-39.0)	23.3 (4.0) 22.6 (15.9-35.9)	-0.13
Height, cm	Mean (SD) Median (range)	111.8 (7.7) 113.1 (94.4-124.0)	111.9 (7.6) 111.3 (99.0-142.0)	112.9 (5.2) 113.0 (99.0-130.2)	-0.14
BMI, kg/m²	Mean (SD) Median (range)	18.1 (2.4) 17.5 (13.2-24.6)	16.8 (2.1) 16.4 (13.7-22.5)	18.2 (2.1) 17.5 (13.7-22.5)	-0.06

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)

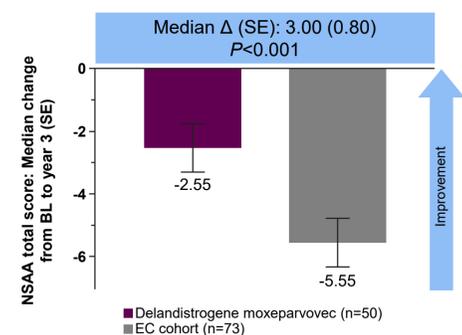### Figure 5. 3-year median change from baseline in NSAA total score

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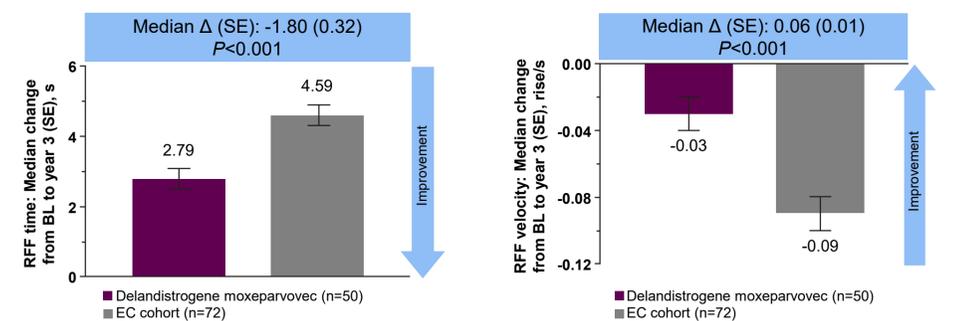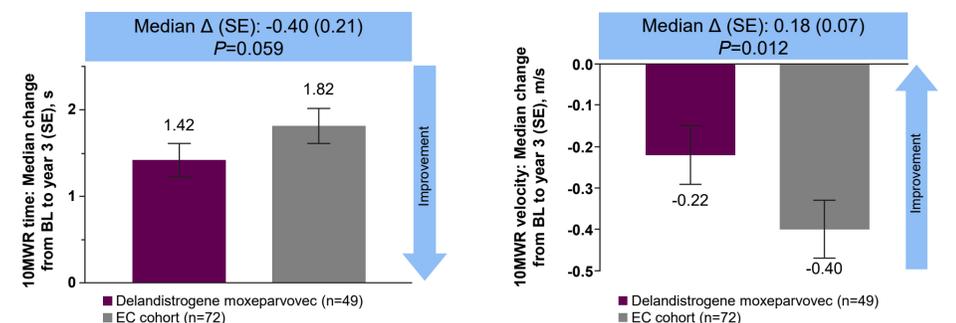

Figure 7. 3-year median changes from baseline in 10MWR time and velocity

Conclusions

- At 3 years, patients treated with delandistrogene moxeparvovec 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 moxeparvovec has a clinically meaningful long-term impact on the disease course of DMD, modifying its trajectory relative to the natural history of the disease

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.

References

1. Mendell JR, et al. JAMA Neurol. 2020;77:1122-1131.
2. Asher DR, et al. Expert Opin Biol Ther. 2020;20:263-274.
3. Zheng C and Baum BJ. Methods Mol Biol. 2008;434:205-219.
4. Mendell JR, et al. Pediatr Neurol. 2024;153:11-18.
5. Proud CM, et al. Poster presented at: Muscular Dystrophy Association (MDA) Clinical and Scientific Conference 2023; March 19-22, 2023; Dallas, TX. Poster 106.
6. ClinicalTrials.gov identifier: NCT03375164. Updated November 14, 2024. Accessed February 23, 2025. https://www.clinicaltrials.gov/study/NCT03375164.
7. ClinicalTrials.gov identifier: NCT03769116. Updated November 14, 2024. Accessed February 23, 2025. https://www.clinicaltrials.gov/study/NCT03769116.
8. ClinicalTrials.gov identifier: NCT04626674. Updated August 26, 2024. Accessed February 23, 2025. https://www.clinicaltrials.gov/study/NCT04626674.
9. ClinicalTrials.gov identifier: NCT01603407. Updated August 12, 2022. Accessed February 23, 2025. https://clinicaltrials.gov/study/NCT01603407.
10. ClinicalTrials.gov identifier: NCT01865804. Updated December 8, 2017. Accessed February 23, 2025. https://clinicaltrials.gov/study/NCT01753804.
11. ClinicalTrials.gov identifier: NCT00468832. Updated April 21, 2016. Accessed February 23, 2025. https://clinicaltrials.gov/study/NCT00468832.
12. Duan D. Mol Ther. 2018;26:2337-2356.
13. Deng J, et al. Front Pharmacol. 2022;13:950651.

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

3-Year Functional Outcomes of Patients With Duchenne Muscular Dystrophy: Pooled Delandistrogene Moxeparvovec Clinical Trial Data vs External Controls
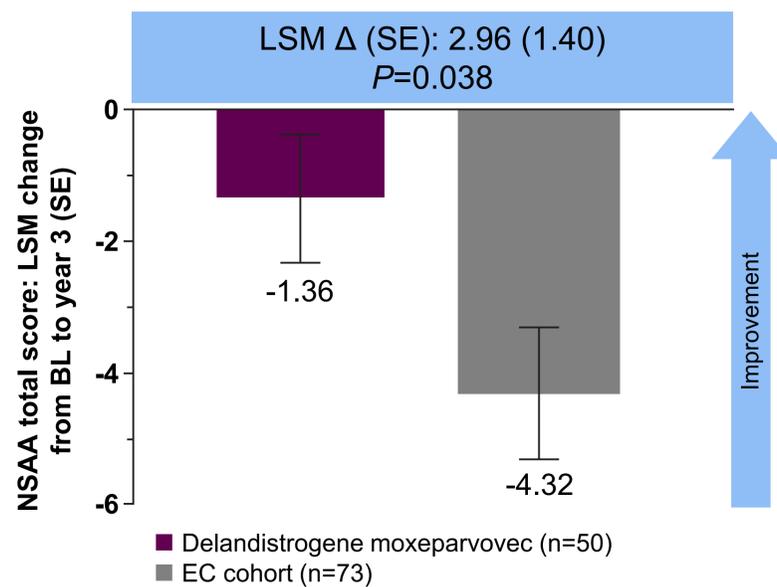
Jerry R. Mendell[1]; Anne M. Connolly[2]; John Day[3]; Craig M. McDonald[4]; Crystal M. Proud[5]; Perry Shieh[6]; Craig M. Zaidman[7]; Matthew Furgerson[1]; Kai Ding[1]; Carol Reid[8]; Alexander P. Murphy[8]; Louise R. Rodino-Klapac[1]

[1]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]Chief of Neurology Division, Nationwide Children's Hospital, Columbus, OH, USA, and Professor of Pediatrics at The Ohio State University College of Medicine, Columbus, OH, USA; [3]Professor, of Neurology and Neurological Sciences (Adult Neurology), of Pediatrics (Genetics) and, by courtesy, of Pathology, Stanford University, Palo Alto, CA, USA; [4]Chair, Department of Physical Medicine & Rehabilitation and Professor, Departments of Pediatrics and Physical Medicine & Rehabilitation, UC Davis, Davis, CA, USA; [5]Pediatric Neurologist and Director of Neurology, Children's Hospital of The King's Daughters, Norfolk, VA, USA; [6]Neurologist, UCLA Health, Los Angeles, CA, USA; [7]Professor of Neurology and of Pediatrics, Washington University in St. Louis, St. Louis, MO, USA; [8]Roche Products Ltd, Welwyn Garden City, UK
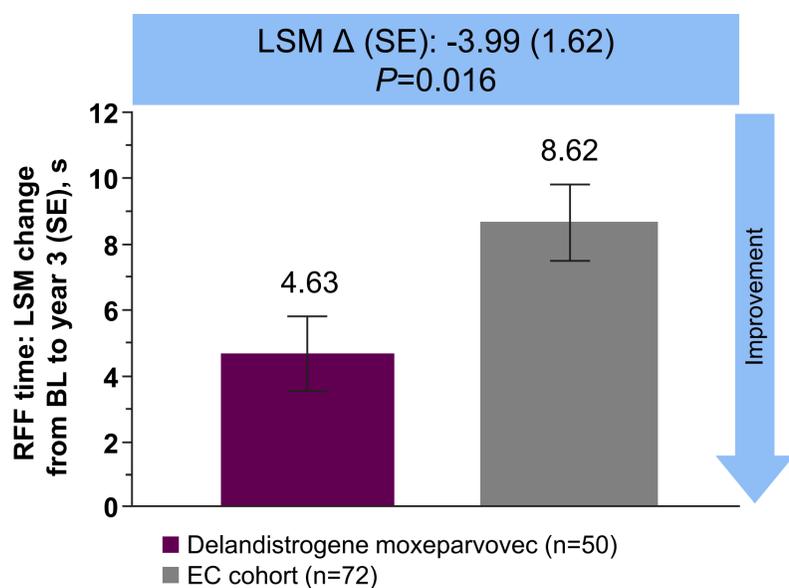Corresponding email address: medinfo@sarepta.com

SUPPLEMENTARY INFORMATION

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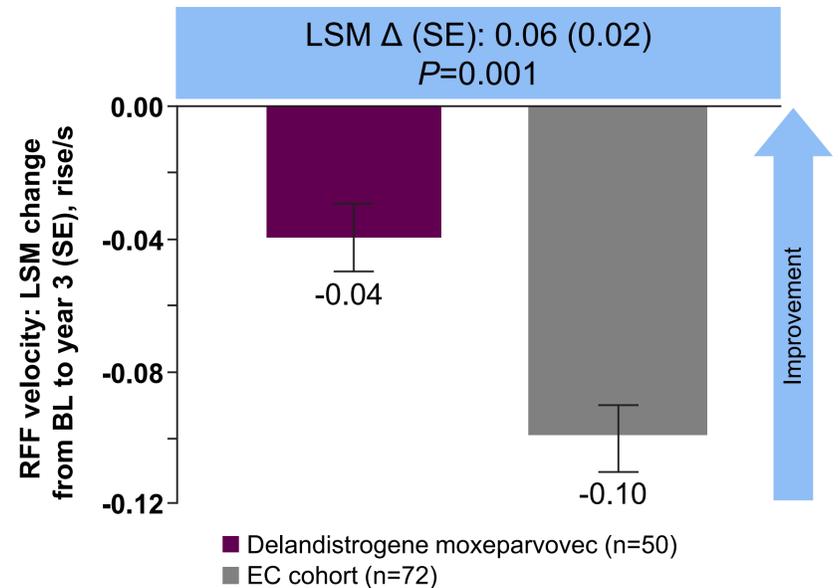## Changes in NSAA Total Score, RFF Time and Velocity, and 10MWR Time and Velocity (MMRM)
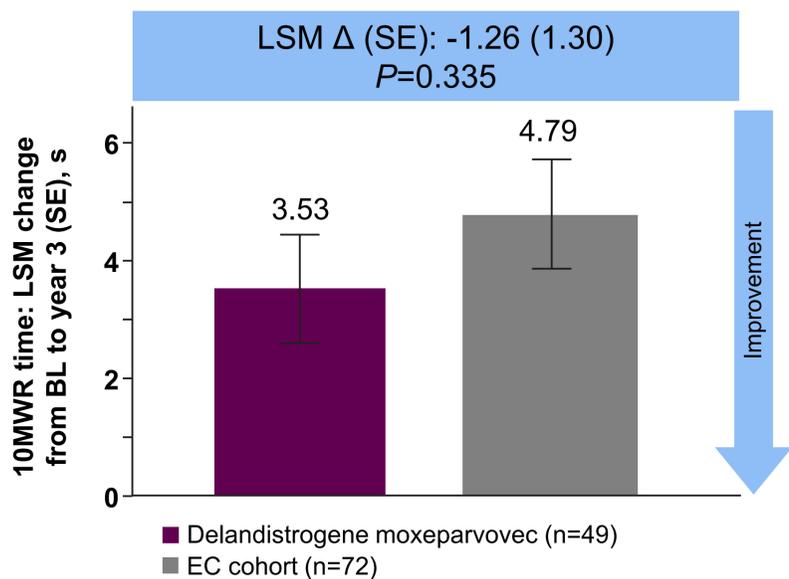

NSAA Total Score

LSM Δ (SE): 2.96 (1.40)
P=0.038

- Delandistrogene moxeparvovec (n=50): -1.36
- EC cohort (n=73): -4.32

RFF Time

LSM Δ (SE): -3.99 (1.62)
P=0.016

- Delandistrogene moxeparvovec (n=50): 4.63
- EC cohort (n=72): 8.62

RFF Velocity

LSM Δ (SE): 0.06 (0.02)
P=0.001

- Delandistrogene moxeparvovec (n=50): -0.04
- EC cohort (n=72): -0.10

10MWR Time

LSM Δ (SE): -1.26 (1.30)
P=0.335

- Delandistrogene moxeparvovec (n=49): 3.53
- EC cohort (n=72): 4.79

10MWR Velocity

LSM Δ (SE): 0.32 (0.12)
P=0.009

- Delandistrogene moxeparvovec (n=49): -0.23
- EC cohort (n=72): -0.55