1350

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

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

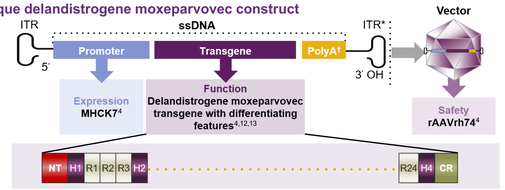
Objective

- 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



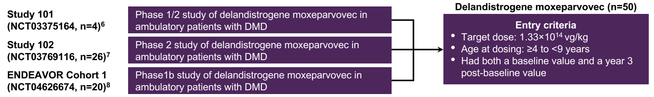
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (ie, copies) it.

Methods

Analysis set

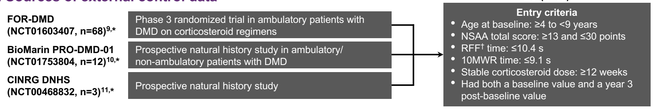
- Functional outcomes data were pooled from 50 patients with DMD enrolled in 3 studies (**Figure 2**)

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



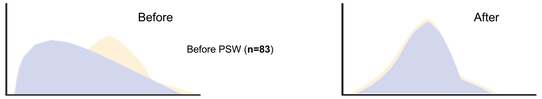
*Only the patients who were receiving a stable corticosteroid regimen were included in the EC cohort. †May also be referred to as TTR.

Methods (cont.)

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
  - RFF
  - Height
  - BMI
  - NSAA total score
  - 10MWR
  - Weight
- 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*



*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

Results (cont.)

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

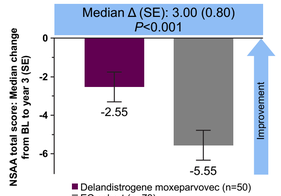


Figure 6. 3-year median change from baseline in RFF time and velocity

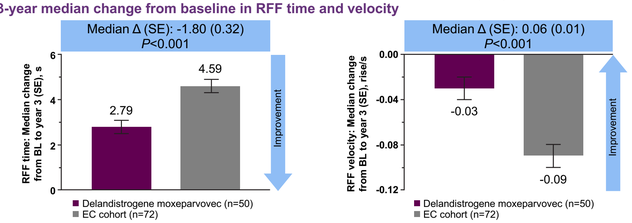
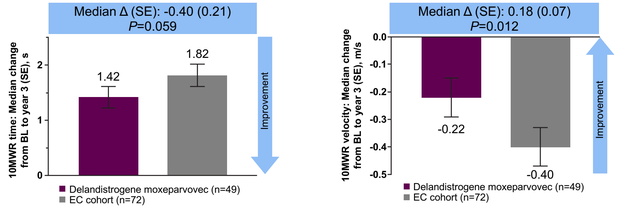


Figure 7. 3-year median changes from baseline in 10MWR time and velocity



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

Acknowledgments

The authors would like to thank the patients, their families, the investigators, and trial staff for their participation in the delandistrogene moxeparvovec studies. Studies 101 and 102 and ENDEAVOR are sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. ENDEAVOR is also funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing and editorial assistance were provided by Srividya Venkitachalam, PhD (HCG), in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and were funded by Sarepta Therapeutics Inc., Cambridge, MA, USA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Disclosures

JM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. **JM** is a co-inventor of AAVrh74.MHCK7.micro-dys technology. **AMC** has received study funding from Sarepta paid to Nationwide Children's Hospital and has served on advisory boards for Sarepta and Edgewise and DMSB for Avidity Biosciences. **JD** reports grants from AMO, Audentes, Avidity, Biogen, Cytokinetics, Ionis Pharmaceuticals, Novartis Gene Therapies, Roche Pharmaceuticals, Sanofi-Genzyme, Sarepta Therapeutics, and Scholar Rock. **JD** participates on advisory boards and is a consultant for Affinia Therapeutics, AMO Pharmaceuticals, Astellas Gene Therapies, Audentes Therapeutics, Avidity Therapeutics, Biogen, Cytokinetics, Epirium Bio, Ionis Pharmaceuticals, Kate Therapeutics, Novartis, Novartis Gene Therapies, Pfizer, Roche/Genentech Pharmaceuticals, Sarepta Therapeutics, Scholar Rock, Shift Therapeutics, and Vertex. **JD** participated in the PepGen Scientific Advisory Board (2021). **JD** was a paid advisor to the Muscular Dystrophy Association and an unpaid advisor to the Myotonic Dystrophy Foundation, Cure SMA, SMA Foundation, Parents Project Muscular Dystrophy, Foundation Building Strength for Nemaline Myopathy, Cure CMD, and Solve FSHD. **JD** holds patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931). **CM** reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other support from Capricor, Catabasis, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. **CP** participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock. **PS** reports being a consultant/independent contractor for AveXis, Biogen, Cytokinetics, and Sarepta Therapeutics and receiving grants/research support from AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Sanofi Genzyme, and Sarepta Therapeutics. **CZ** receives research support from Biogen and Novartis, serves on an advisory board for Biogen, receives speaker fees from Sarepta Therapeutics, and was a paid consultant for Optum. **LRK** is an employee of Sarepta Therapeutics and has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology. **JM**, **MF**, **KD**, and **SE** are employees of Sarepta Therapeutics Inc., and may own stock and / or stock options in the company. **CR** and **APM** are employees of F. Hoffmann-La Roche Ltd and may have stock options. Previously presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference; March 16-19, 2025; Dallas, TX, USA.

Abbreviations

10MWR, 10-meter walk/run; **rAAVrh74**, recombinant adeno-associated virus rhesus isolate serotype 74; **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; **poly A**, polyadenylation; **PSW**, propensity-score weighting; **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; March19-22, 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. https://clinicaltrials.gov/study/NCT01603407.
10. ClinicalTrials.gov identifier: NCT01865604. 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.

Presented at the American Society of Gene and Cell Therapy (ASGCT) 28th Annual Meeting; May 13-17, 2025; New Orleans, LA, USA.

1350

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

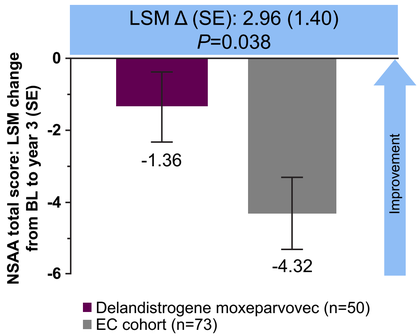
Jerry Mendell[1]; Anne M. Connolly[2]; John Day[3]; Craig McDonald[4]; Crystal Proud[5]; Perry Shieh[6]; Craig Zaidman[7]; Matthew Furgerson[1]; Sravya Ennamuri[1]; Kai Ding[1]; Carol Reid[8]; Alexander P. Murphy[8]; Louise Rodino-Klapac[1]

[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

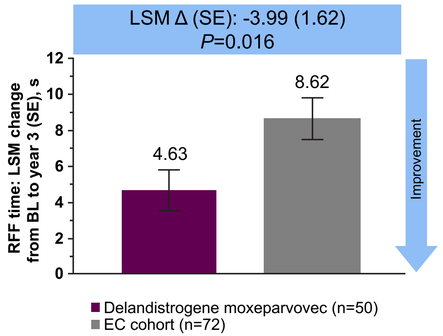
Supplementary Information

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

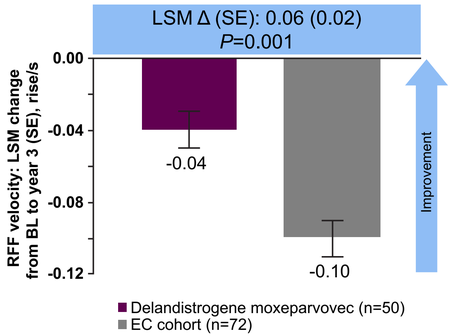
NSAA Total Score



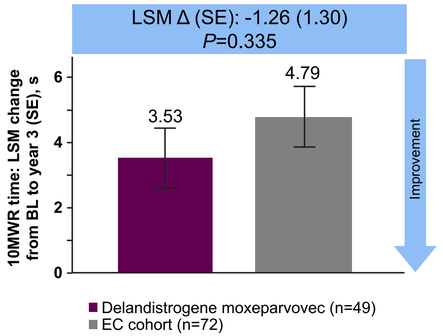
RFF Time



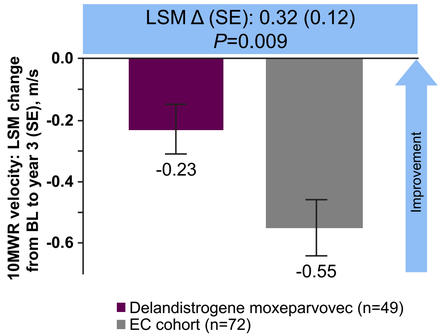
RFF Velocity



10MWR Time



10MWR Velocity



Acknowledgments

The authors would like to thank the patients, their families, the investigators, and trial staff for their participation in the delandistrogene moxeparvovec studies. Studies 101 and 102 and ENDEAVOR are sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. ENDEAVOR is also funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing and editorial assistance were provided by Srividya Venkitachalam, PhD (HCG), in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and were funded by Sarepta Therapeutics Inc., Cambridge, MA, USA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Disclosures

JM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. **JM** is a co-inventor of AAVrh74.MHCK7.micro-dys technology. **AMC** has received study funding from Sarepta paid to Nationwide Children's Hospital and has served on advisory boards for Sarepta and Edgewise and DMSB for Avidity Biosciences. **JD** reports grants from AMO, Audentes, Avidity, Biogen, Cytokinetics, Ionis Pharmaceuticals, Novartis Gene Therapies, Roche Pharmaceuticals, Sanofi-Genzyme, Sarepta Therapeutics, and Scholar Rock. **JD** participates on advisory boards and is a consultant for Affinia Therapeutics, AMO Pharmaceuticals, Astellas Gene Therapies, Audentes Therapeutics, Avidity Therapeutics, Biogen, Cytokinetics, Epirium Bio, Ionis Pharmaceuticals, Kate Therapeutics, Novartis, Novartis Gene Therapies, Pfizer, Roche/Genentech Pharmaceuticals, Sarepta Therapeutics, Scholar Rock, Shift Therapeutics, and Vertex. **JD** participated in the PepGen Scientific Advisory Board (2021). **JD** was a paid advisor to the Muscular Dystrophy Association and an unpaid advisor to the Myotonic Dystrophy Foundation, Cure SMA, SMA Foundation, Parents Project Muscular Dystrophy, Foundation Building Strength for Nemaline Myopathy, Cure CMD, and Solve FSHD. **JD** holds patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931). **CM** reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other support from Capricor, Catabasis, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. **CP** participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock. **PS** reports being a consultant/independent contractor for AveXis, Biogen, Cytokinetics, and Sarepta Therapeutics and receiving grants/research support from AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Sanofi Genzyme, and Sarepta Therapeutics. **CZ** receives research support from Biogen and Novartis, serves on an advisory board for Biogen, receives speaker fees from Sarepta Therapeutics, and was a paid consultant for Optum. **LRK** is an employee of Sarepta Therapeutics and has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology. **JM**, **MF**, **KD**, and **SE** are employees of Sarepta Therapeutics Inc., and may own stock and / or stock options in the company. **CR** and **APM** are employees of F. Hoffmann-La Roche Ltd and may have stock options. Previously presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference; March 16-19, 2025; Dallas, TX, USA.

Abbreviations

10MWR, 10-meter walk/run; **rAAVrh74**, recombinant adeno-associated virus rhesus isolate serotype 74; **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; **poly A**, polyadenylation; **PSW**, propensity-score weighting; **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; March19-22, 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. https://clinicaltrials.gov/study/NCT01603407.
10. ClinicalTrials.gov identifier: NCT01865864. 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.

Presented at the American Society of Gene and Cell Therapy (ASGCT) 28th Annual Meeting; May 13-17, 2025; New Orleans, LA, USA.