Abstract #354

Phase 1/2a trial of delandistrogene moxeparvovec in patients with DMD: 4-year update

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***Presenting on behalf of the authors (email address: medinfo@sarepta.com)**

Presented at the 26th Annual Meeting of the American Society of Gene + Cell Therapy (ASGCT) Los Angeles, CA, USA | May 16–20, 2023

Acknowledgments and disclosures

Acknowledgments

- The authors would like to thank the patients and their families for their participation in Study 101 (SRP-9001-101; NCT03375164), as well as the investigators and trial staff involved in Study 101
- Study 101 is sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA
- Medical writing and editorial support were provided by Ayesha Babar, MSc, of Nucleus Global, 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
- These data are an encore of data first presented by J.R. Mendell at the 17th International Congress on Neuromuscular Diseases 2022

Disclosures

- LPL reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials and licensing fees for natural history data
- JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.SRP-9001-dys technology
- ZS has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy
- KJL has received an institutional grant from Sarepta Therapeutics
- NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials
- MAI, KC, RS and MJH have nothing to disclose
- LNA reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials
- SL, RAP, DAG, ERP, LH, SM, ED and LRRK are employees of Sarepta Therapeutics and may own stocks or have stock options
- LRRK is an employee of Sarepta Therapeutics, 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.SRP-9001-dys technology

Objectives and overview

- This Phase 1/2a, single-dose, open-label clinical trial (Study 101; SRP-9001-101; NCT03375164)[1] evaluated the safety of systemic delivery of delandistrogene moxeparvovec (SRP-9001) in patients with DMD (≥4 to <8 years old)
  - We provide a 4-year update on long-term safety and functional data from four patients treated with delandistrogene moxeparvovec
  - To put the results into context, a post hoc analysis was conducted to compare the 4-year data from Study 101 with data from a propensity-score-weighted EC cohort

What does this study mean for the DMD community?

The single-dose gene transfer therapy delandistrogene moxeparvovec **generally led to improvements** in functional measures over 4 years in patients with DMD and had a **long-term acceptable safety profile**

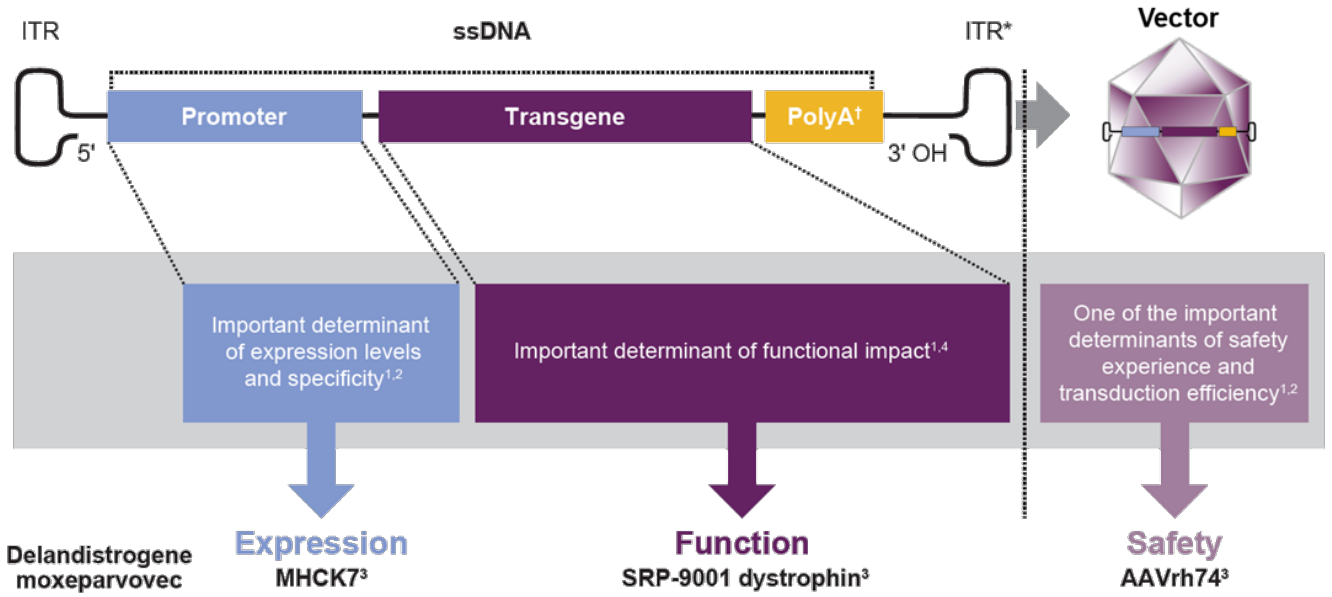
Results provide proof-of-concept support for the continuation of clinical trials to assess the safety and efficacy of the SRP-9001 transgene in patients with DMD

DMD, Duchenne muscular dystrophy; EC, external control.

1. ClinicalTrials.gov. NCT03375164 (Accessed March 2023).

Background

- Delandistrogene moxeparvovec is an investigational rAAV vector-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding SRP-9001 dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein[1–3]



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

AAVrh74, adeno-associated virus rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; OH, hydroxyl; PolyA, polyadenylation; rAAV, recombinant adeno-associated virus; ssDNA, single-stranded DNA.

1. Asher DR, et al. *Expert Opin Biol Ther*. 2020; 20:263–274; 2. Zheng C and Baum BJ. *Methods Mol Biol*. 2008; 434:205–219; 3. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131; 4. Chandler RJ and Venditti CP. *Transl Sci Rare Dis*. 2016; 1:73–89.

Study design: Study 101

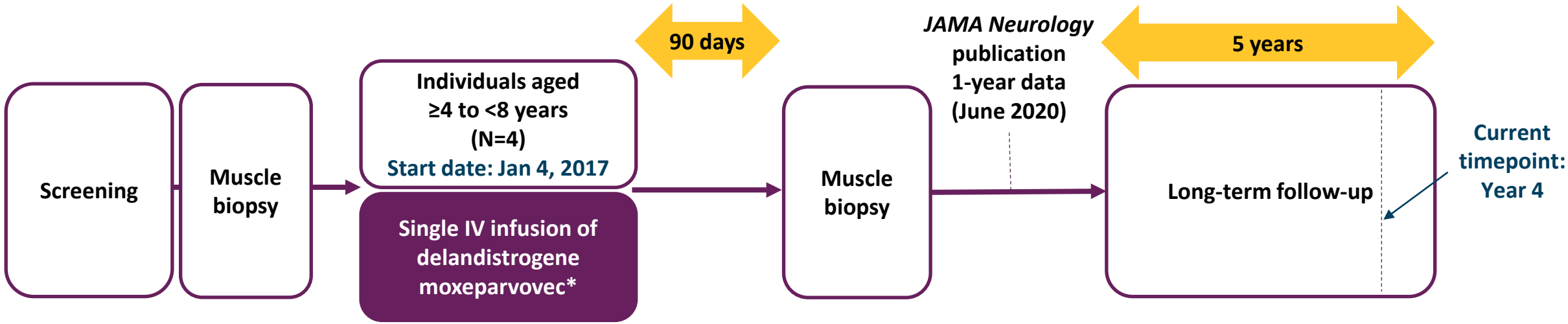
Open-label Phase 1/2a trial in patients with DMD ≥4 to <8 years old

Primary outcome measure:

- Safety based on the number of participants with AEs

Key additional outcome measures:

- SRP-9001 dystrophin expression in pre- and post-muscle biopsy at 12 weeks post-infusion (Day 90): IF and WB
- Change from baseline in NSAA and TFTs: 100MWR, 4-stair Climb, 10MWR and Time to Rise



*All patients received one IV infusion in the peripheral limb vein at the dose 2.0×10^{14} vg/kg determined by supercoiled qPCR method (1.33×10^{14} vg/kg linear qPCR equivalent), and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery.

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AE, adverse event; DMD, Duchenne muscular dystrophy; IF, immunofluorescence; IV, intravenous; NSAA, North Star Ambulatory Assessment; qPCR, quantitative polymerase chain reaction; TFT, timed function test; vg, vector genome; WB, western blot.

1. ClinicalTrials.gov. NCT03375164 (Accessed March 2023).

Baseline demographics[1]

	Patient 1	Patient 2	Patient 3	Patient 4
Age at screening, years	5.7	4.8	6.0	4.0
Height, cm	109.9	104.3	110.0	95.7
Weight, kg	18.4	18.9	21.4	13.7
BMI, kg/m²*	15.2	17.4	17.7	15.0
NSAA, total score	18.0	19.0	26.0	19.0

*Note that all patients have a BMI of less than 18.5.

BMI, body mass index; NSAA, North Star Ambulatory Assessment.

1. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131.

Study 101: 4-year data
*Primary endpoint: Safety**

There were no SAEs or discontinuations from the study

TRAEs were mild or moderate and all resolved

- TRAEs occurred mostly within the first 70 days of treatment
- The most common TRAE was vomiting (9 of 18 TRAEs)
  - Patients had transient vomiting generally within the first week post-infusion
  - TRAEs of vomiting did not correlate with liver enzyme elevations or any other abnormalities

There were no serious abnormalities observed in hematologic and chemistry panels

- Three patients had elevated GGT in the first 3 months post-treatment, which resolved with oral steroid treatment
  - These changes were asymptomatic, and no patients were hospitalized

None of the AEs were associated with complement activation

No other clinically significant laboratory findings were reported

*Up to data cut-off: 26 Apr 2022.
AE, adverse event; GGT, γ-glutamyl transpeptidase; SAE, serious AE; TRAE, treatment-related AE.
Roche/Sarepta data on file (2023).

Functional outcomes
NSAA total scores over 4 years post-treatment

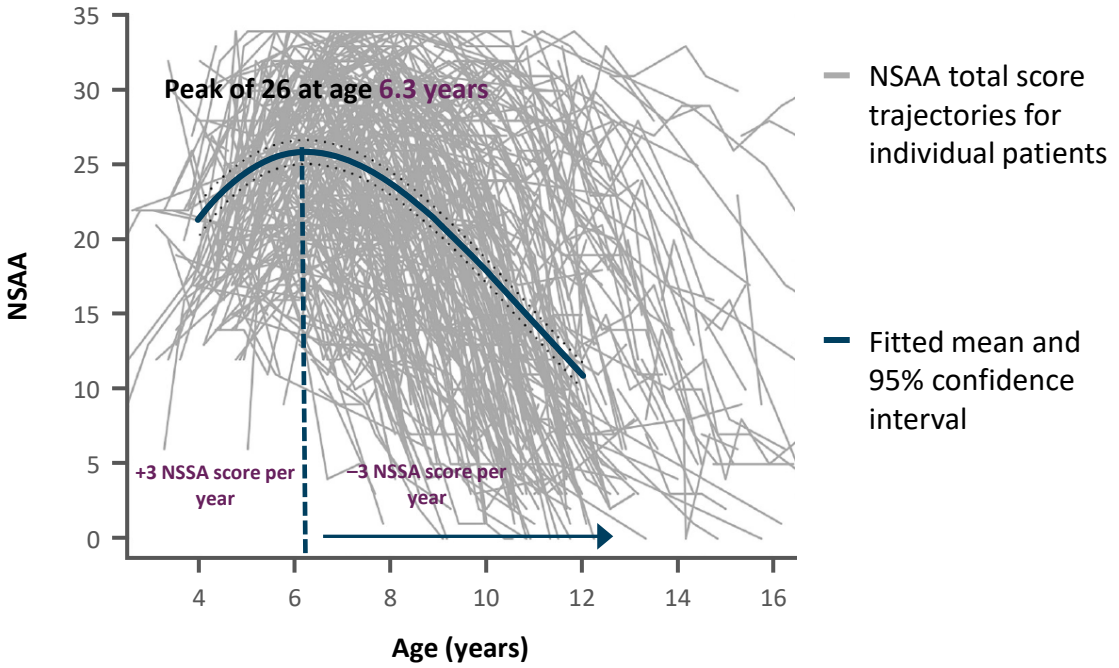
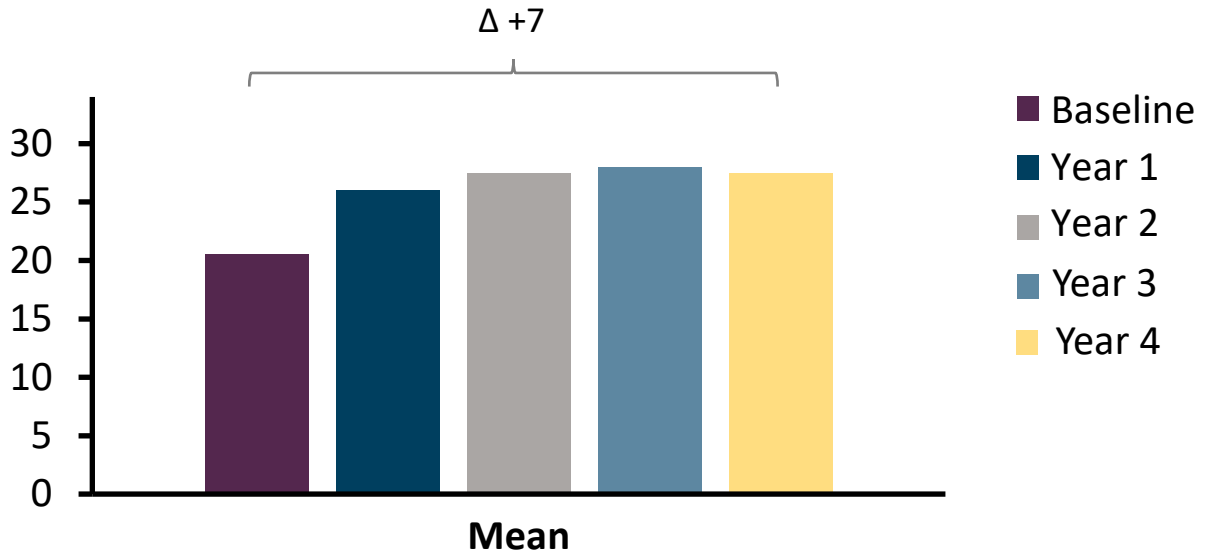


Figure adapted from Muntoni F, et al 2019[1]

Mean change in NSAA total score* from baseline to Year 4: +7

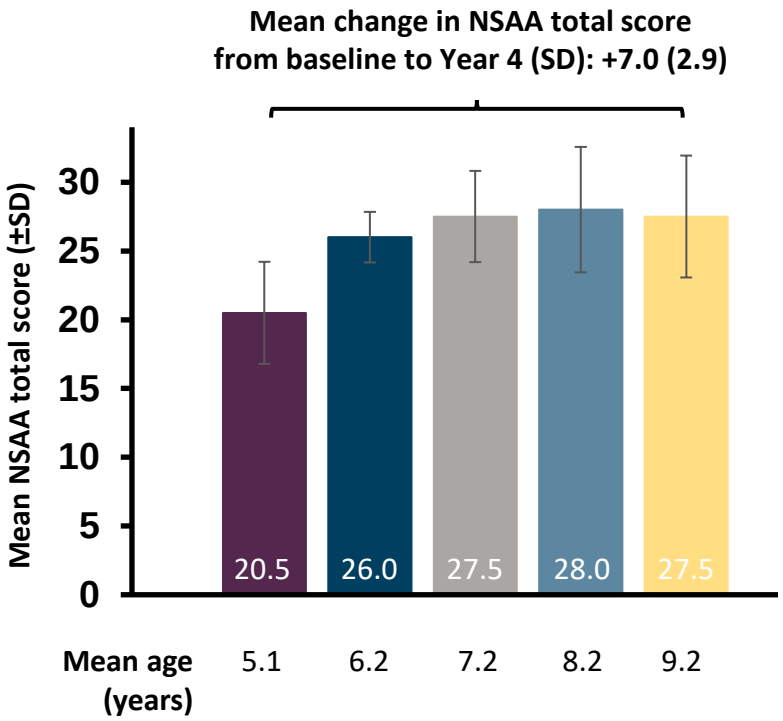


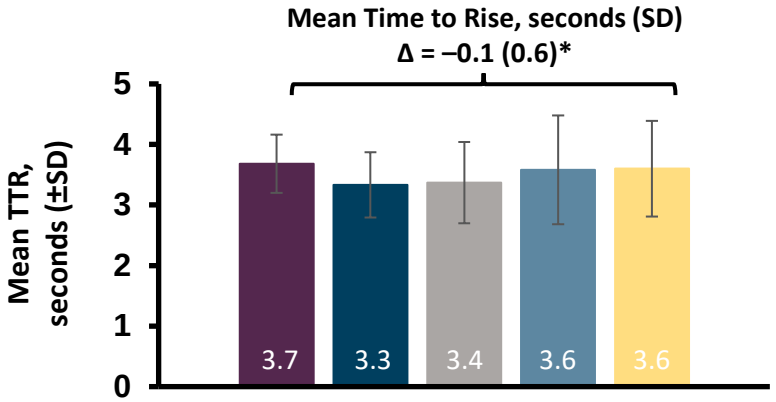
Mean total NSAA score declines after the age of 6 years in patients with DMD[1]

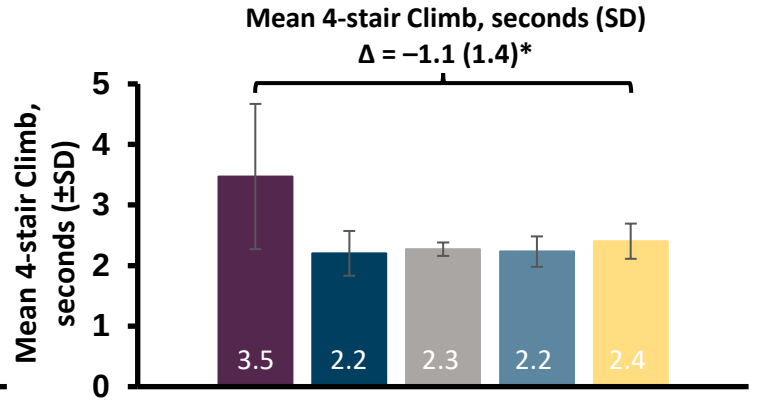
Mean age was 5.1 years at baseline† and 9.2 years at Year 4

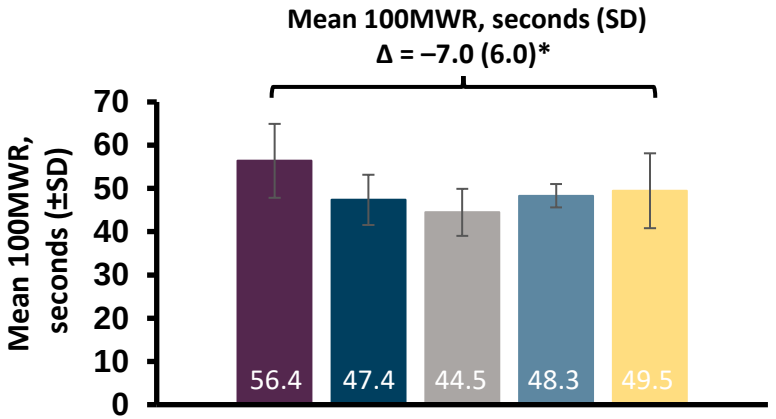
*Three-year NSAA value (Patient 2) and 2-year NSAA value (Patient 4) were from a remote assessment due to COVID-19-related restrictions at the site. †Age at baseline NSAA assessment.
DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.
1. Muntoni F, et al. *PLoS One*. 2019; 14:e0221097.

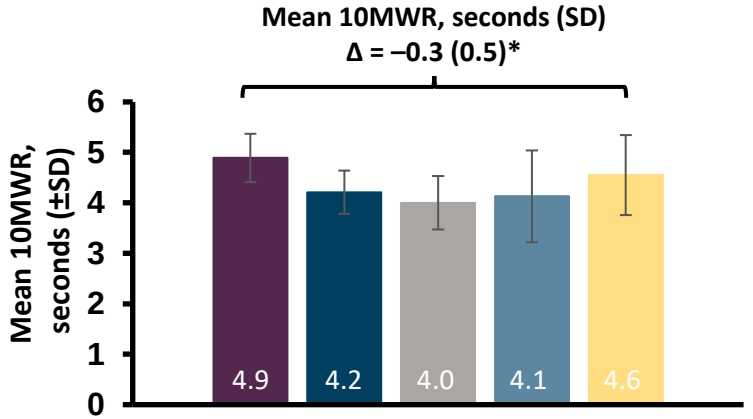
Functional outcomes
Summary of 4-year TFTs







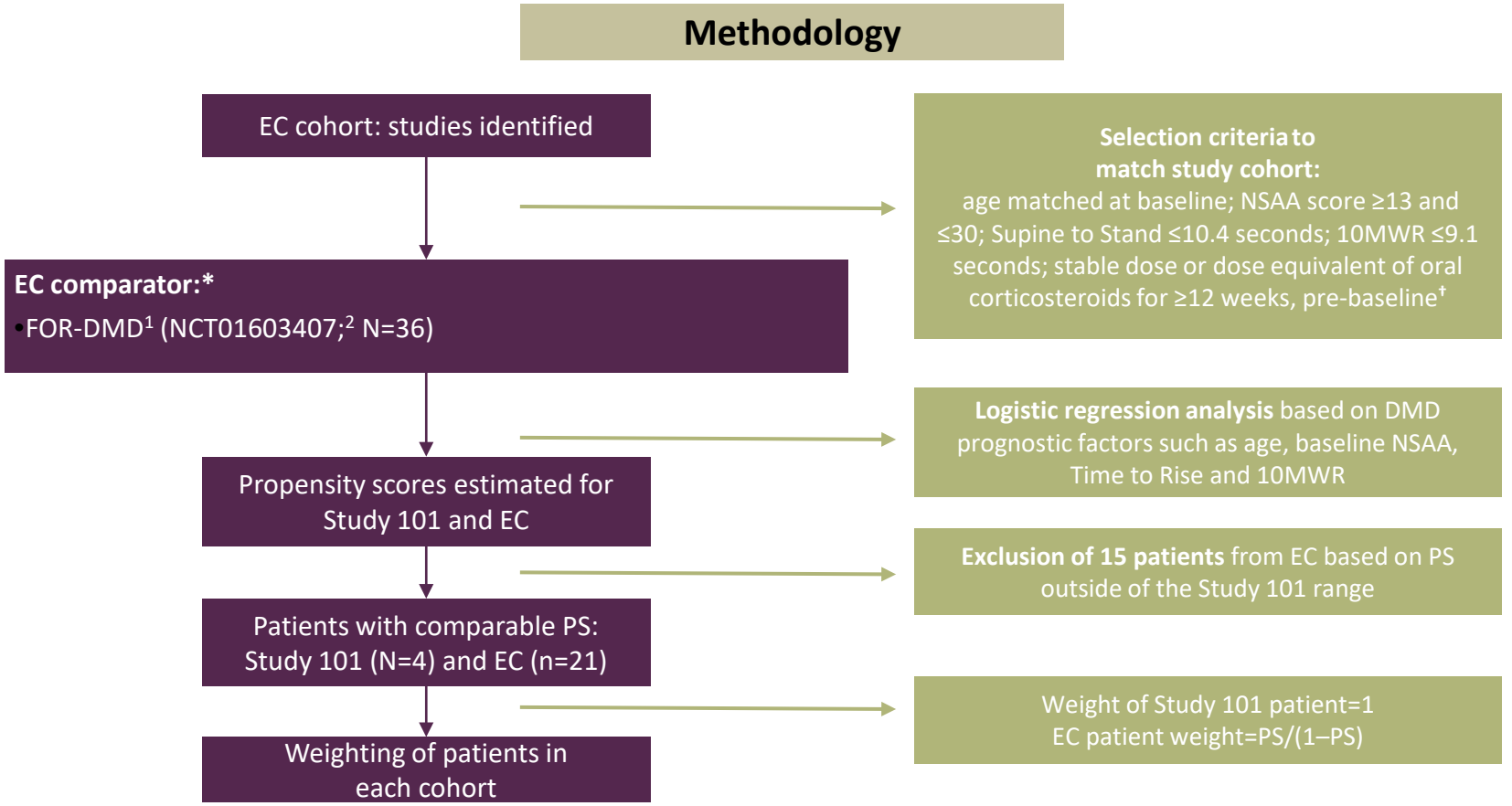




*Negative values indicate an improvement in the time taken to achieve this endpoint.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; NSAA, North Star Ambulatory Assessment; SD, standard deviation; TFT, timed function test; TTR, Time to Rise.
Roche/Sarepta data on file (2023).

Post hoc analysis: Study 101 4-year data versus a propensity-score-weighted EC

- Well-matched, natural history control cohorts and disease models can play a critical role in examining the treatment effect in clinical trials of progressive, heterogeneous, neuromuscular diseases
- **Propensity-score-weighted analysis ensures maximum comparability between this external cohort and the delandistrogene moxeparvovec groups**



*N=36 before propensity-score weighting. After excluding subjects with non-overlapping propensity scores, n=21. FOR-DMD was a double-blind study comparing three corticosteroid regimens widely used for DMD. Patients on the daily regimen (prednisone or deflazacort) were included as EC patients for the analysis. †Pre-baseline = prior to first functional assessment.
10MWR, 10-meter Walk/Run; DMD, Duchenne muscular dystrophy; EC, external control; FOR-DMD, Finding the optimum regimen for Duchenne Muscular Dystrophy; NSAA, North Star Ambulatory Assessment; PS, propensity score.
1. https://for-dmd.org/en/ (Accessed March 2023); 2. ClinicalTrials.gov. NCT01603407 (Accessed March 2023)/

Baseline comparison of delandistrogene moxeparvovec-treated patients versus propensity-score-weighted EC cohort

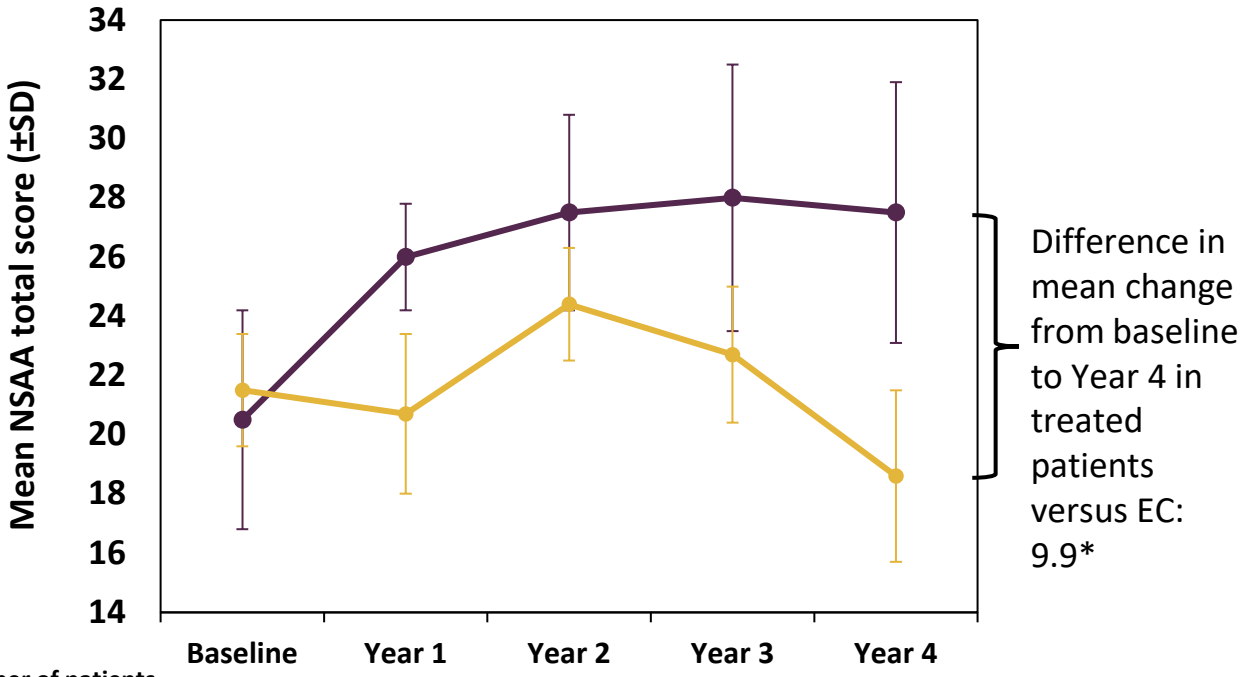
	Delandistrogene moxeparvovec-treated patients (N=4) Mean (SD) Min–Max	EC (n=21)* Mean (SD) Min–Max
Age, years†	5.1 (0.9) 4.0–6.0	6.4 (0.3) 4.9–7.7
NSAA total score	21.0 (3.7) 18.0–26.0	22.0 (1.9) 13.0–30.0
Time to Rise, seconds	3.7 (0.5) 3.0–4.1	3.9 (0.4) 2.6–7.4
10-meter Walk/Run, seconds	4.9 (0.5) 4.3–5.4	5.0 (0.3) 3.6–6.7

Differences between the cohort of patients treated with delandistrogene moxeparvovec and the EC cohort were not statistically significant

*N=36 before propensity-score weighting. After excluding subjects with non-overlapping propensity scores, n=21. †Age at first assessment.
EC, external control; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

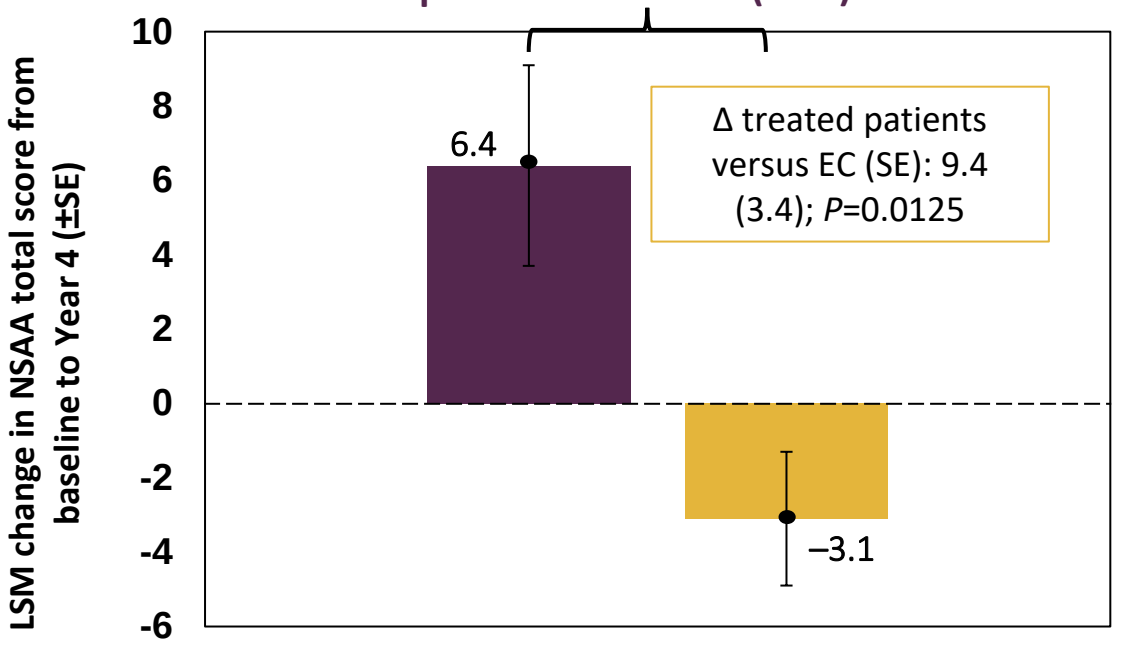
NSAA total score across 4 years post-treatment with delandistrogene moxeparvovec versus propensity-score-weighted EC cohort

NSAA total score over 4 years in treated patients versus EC (descriptive means)



Number of patients	Baseline	Year 1	Year 2	Year 3	Year 4
Delandistrogene moxeparvovec	4	4	4	4	4
EC	21	21	19	20	21

Change in NSAA total score from baseline to Year 4 in treated patients versus EC (LSM)



Delandistrogene moxeparvovec (N=4)

Propensity-score-weighted EC (n=21)

*NSAA change from baseline to Year 4 in treated patients versus EC calculated using descriptive means, based on propensity-score weighting.

EC, external control; LSM, least squares mean; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error.

Study 101 summary

- TRAEs mostly occurred in the first 70 days post-infusion, and all resolved
- Functional assessments demonstrated clinically meaningful improvement in motor function that was sustained long term, and importantly, at ages when functional decline is expected based on natural history
- NSAA improvements were generally accompanied by improvement in TFTs over 4 years
- Stabilized improvement in motor function 4 years post-treatment with delandistrogene moxeparvovec suggested long-term, durable expression of SRP-9001 dystrophin protein in target muscle

Four-year data from Study 101 reinforced that a single, intravenous administration of delandistrogene moxeparvovec is well tolerated, with no new safety signals identified

The safety profile and durable response provide proof-of-concept support for continued clinical trials to assess delandistrogene moxeparvovec in patients with DMD

DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; TFT, timed function test; TRAE, treatment-related adverse event.

Muntoni F, et al. *PLoS One*. 2019; 14:e0221097.