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

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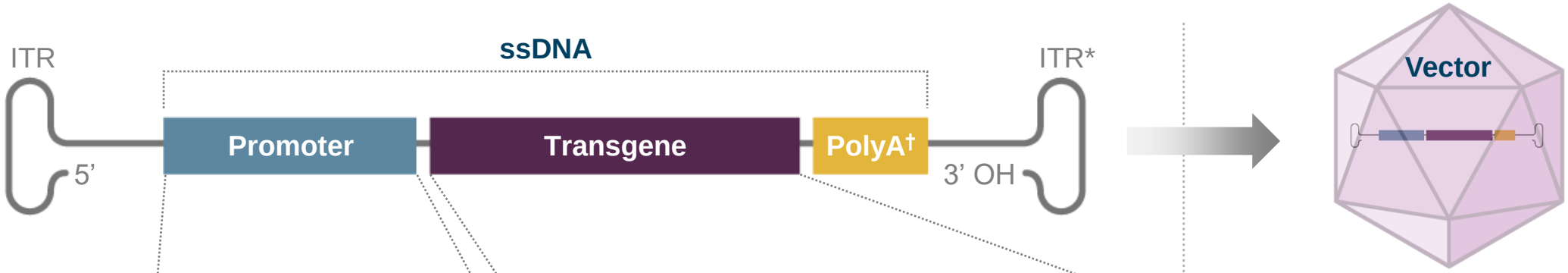
Acknowledgements and disclosures

- This study was funded by Sarepta Therapeutics
- Delandistrogene moxeparvovec (SRP-9001) is an investigational therapy and has not been reviewed or approved by the FDA
- Trial registration: NCT03375164
- The authors would like to thank the patients and their families for their participation in Study 101
- JRM has received study funding from Sarepta Therapeutics for the current presentation and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. In addition, he is a co-inventor of AAVrh74.MHCK7.micro-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
- 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
- NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials
- MAI, KC, RS and MH 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, LH, SM and ED are employees of Sarepta Therapeutics and may have stock options
- LRR-K is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, as well as 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
- Medical writing and editorial support was provided by Marketta Kachemov, PhD of Nucleus Global, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3)

Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed for the treatment of DMD[1–3]

Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin – an engineered, shortened, functional dystrophin 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; MHCK, myosin-heavy-chain kinase; OH, hydroxide; PolyA, polyadenylation; 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 101 (NCT03375164)[1] study design

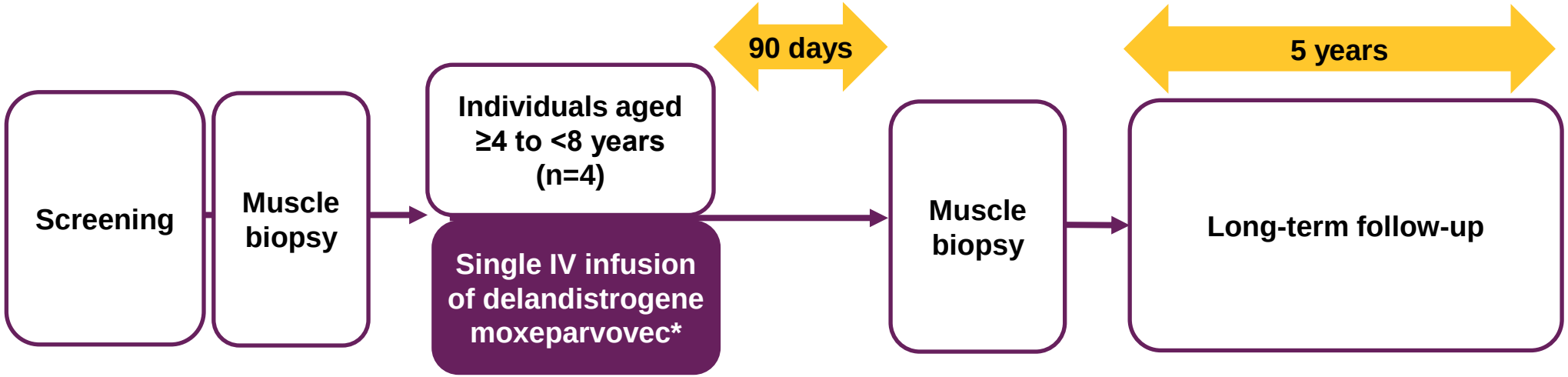
Open-label Phase 1/2a trial in patients with DMD ≥4 to <8 years old

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 in NSAA and TFTs: 100m Timed Test, 4-Stair Climb, 10m Timed Test and Time to Rise



*All patients received one IV infusion in the peripheral limb vein at the dose $2.0x10^{14}$ vg/kg determined by supercoiled qPCR method ($1.33x10^{14}$ vg/kg linear qPCR equivalent), and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery.

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; WB, western blot.

1. ClinicalTrials.gov. NCT03375164 (Accessed June 2022).

Study 101 baseline demographics[1]

	Patient 1	Patient 2	Patient 3	Patient 4
Age at screening, (years)	5	4	6	4
Height, (cm)	109.9	104.3	110.0	95.7
Weight, (kg)	18.4	18.9	21.4	13.7
BMI	15.2	17.4	17.7	15.0
NSAA	18	19	26	19

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

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

Study 101 safety summary*

Generally well tolerated; there were no SAEs or discontinuations from the study

TRAEs were mild or moderate and all resolved

- TRAEs occurred mostly within the first 90 days of treatment
- No TRAEs occurred from the second to the fourth year post-infusion
- 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 abnormality

There were no serious abnormalities observed in haematological and chemistry panels

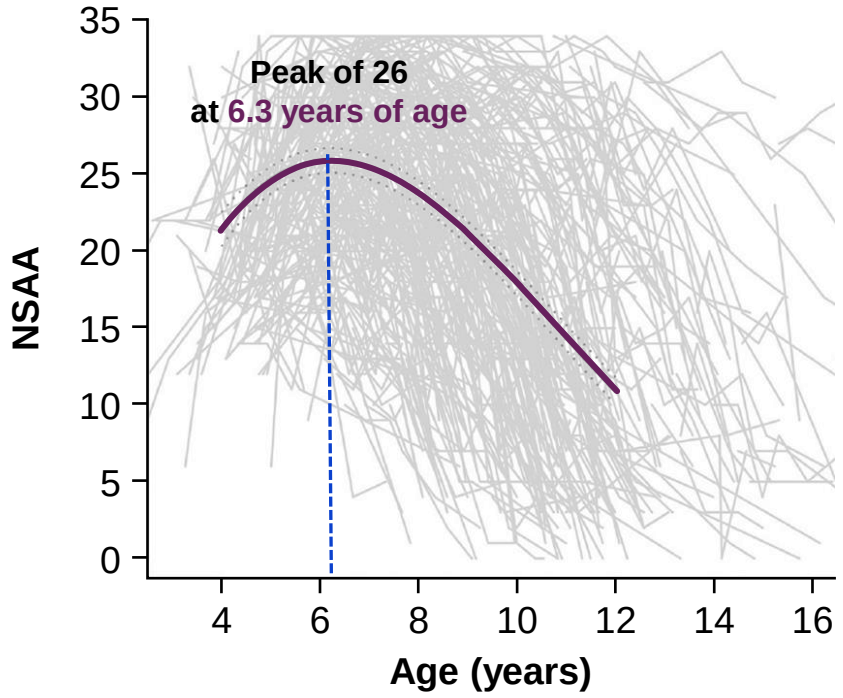
- Three patients had elevated γ-glutamyl transpeptidase in the first 3 months post-treatment, which resolved with oral steroid treatment
  - These changes were asymptomatic, and no patients were hospitalised

None of the AEs were associated with clinical complement activation

No other clinically significant laboratory findings were reported

*Up to data cut-off: 26 Apr 2022.
AE, adverse event; SAE, serious AE; TRAEs, treatment-related AE.

NSAA total score natural history trajectory and NSAA scoring overview[1,2]



NSAA total score trajectories for individual patients

Fitted mean and 95% confidence interval

Mean total NSAA score declines after the age of 6 years in people with DMD

NSAA is a composite endpoint evaluating physical function across 17 tests with increasing difficulty

Score	Ability
2	Able to perform
1	Able to perform with difficulty
0	Unable to Perform

Assessment
Items 14–17: Jump, hop, run
Item 13: Stand on heels
Item 12: Lifts head
Item 11: Rise from floor
Item 10: Gets to sitting
Items 6–9: Climb on and off box step
Items 4 & 5: Stand on one leg
Item 3: Stand up from chair
Item 2: Walk
Item 1: Stand

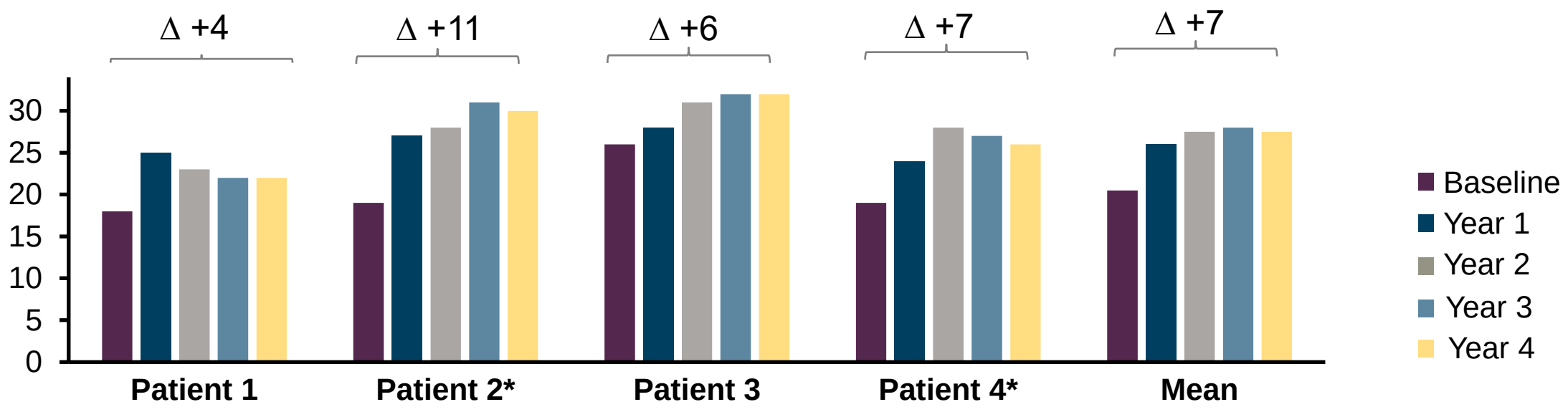
DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.

1. Muntoni F, et al. *PLoS One*. 2019; 14:e0221097; 2. Straub V, et al. *Neuromuscul Disord*. 2018; 28:690–701.

Functional outcomes

NSAA total scores over 4 years after treatment with delandistrogene moxeparvovec

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



	Patient 1	Patient 2*	Patient 3	Patient 4*	Mean
Age (years)					
At baseline†	5.7	4.8	6.0	4.0	5.1
At Year 1	6.8	5.8	7.1	5.1	6.2
At Year 2	7.7	6.8	8.0	6.3	7.2
At Year 3	8.7	7.8	9.1	7.1	8.2
At Year 4	9.7	8.8	10.1	8.1	9.2

*Patient 2: 3-year NSAA value and Patient 4: 2-year NSAA value were from a remote assessment due to COVID-19-related restrictions at the site. †Age at baseline NSAA assessment.
NSAA, North Star Ambulatory Assessment.

Functional outcomes

Summary of 4-year TFTs

	Change from baseline to Year 4				Mean
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**All patients**
Age at Year 4, (years)	9.7	8.8	10.1	8.1	**9.2**
NSAA total score	+4	+11	+6	+7	**+7.0**
Time to Rise, (sec)*	+0.7	–0.3	–0.7	0	**–0.1**
4-Stair Climb, (sec)*	–0.7	–1.7	+0.7	–2.6	**–1.1**
100m, (sec)*	–4.1	–10.1	–0.1	–13.5	**–7.0**
10m run, (sec)*	–0.7	–0.8	+0.3	–0.1	**–0.3**

*Negative values show an improvement in the time taken to achieve this endpoint.
NSAA, North Star Ambulatory Assessment; TFT, timed function test.

Propensity score-weighted external control (EC) cohort pool (N=36*)

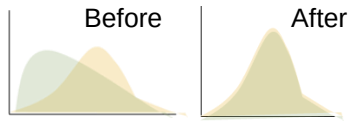
- A post hoc analysis was conducted to contextualise the 4-year data from Study 101 with data from a propensity score-weighted EC cohort
- The control cohort includes external clinical trial data from the FOR-DMD[1†] study (NCT01603407[2]; N=36)
- Similar methodology to the ENDEAVOR study[3] and integrated analyses[4] were used to identify EC patients for this post hoc analysis

Post hoc analysis

Propensity score weighting based on:

- Age
- NSAA
- Time to Rise results
- 10-metre walk/run results

Example EC before and after propensity weighting‡



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*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. ‡Propensity weighting involves taking an EC group with similar age and function, but unequal distribution, and ensuring overlap after propensity weighting. Example EC before and after propensity weighting is shown in the example graphs.
DMD, Duchenne muscular dystrophy; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NSAA; North Star Ambulatory Assessment.
1. https://for-dmd.org/en/ (Accessed June 2022); 2. ClinicalTrials.gov. NCT01603407 (Accessed June 2022); 3. Zaidman C, et al. Presented at ICNMD 2022 poster #eP02.05.01: “One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)”; 4. Zaidman C, et al. Presented at ICNMD 2022 poster #eP02.05.05: “Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD.”

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

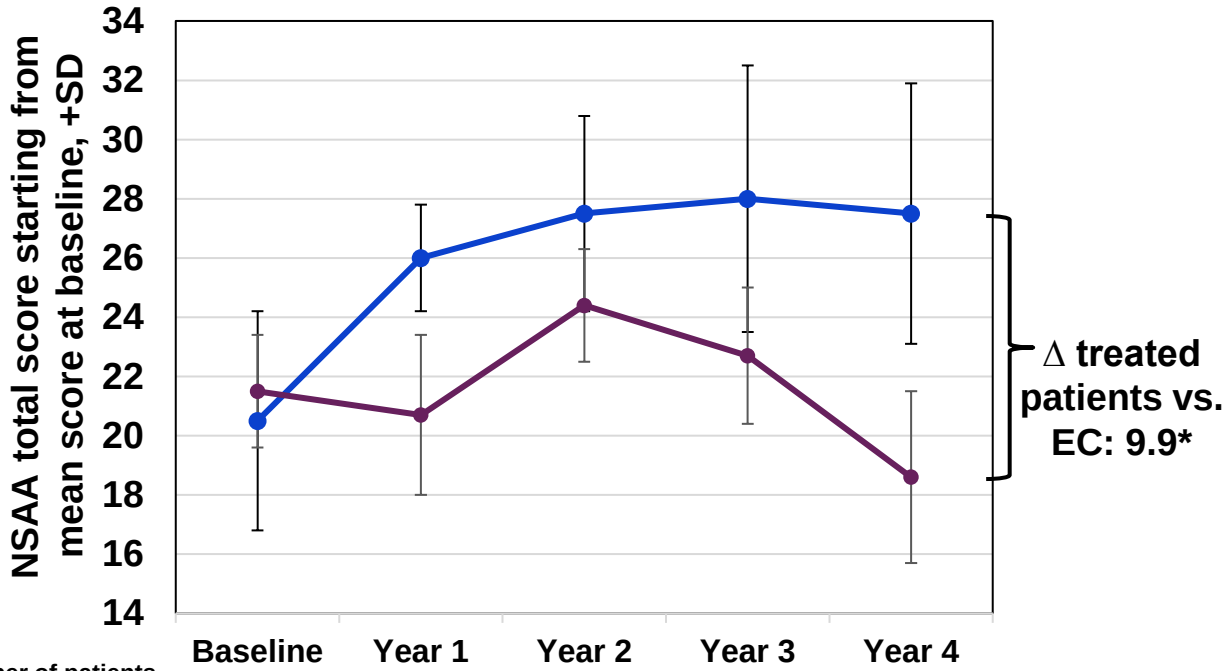
	Statistics	Delandistrogene moxeparvovec-treated patients (N=4)	EC (n=21)*
Age, years†	Mean (SD) Min, max	5.1 (0.9) 4.0, 6.0	6.4 (0.3) 4.9, 7.7
NSAA total score	Mean (SD) Min, max	21 (3.7) 18, 26	22 (1.9) 13, 30
Time to Rise, seconds	Mean (SD) Min, max	3.7 (0.5) 3.0, 4.1	3.9 (0.4) 2.6, 7.4
Time of 10-metre walk/run, seconds	Mean (SD) Min, max	4.9 (0.5) 4.3, 5.4	5.0 (0.3) 3.6, 6.7

*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.

Functional outcomes

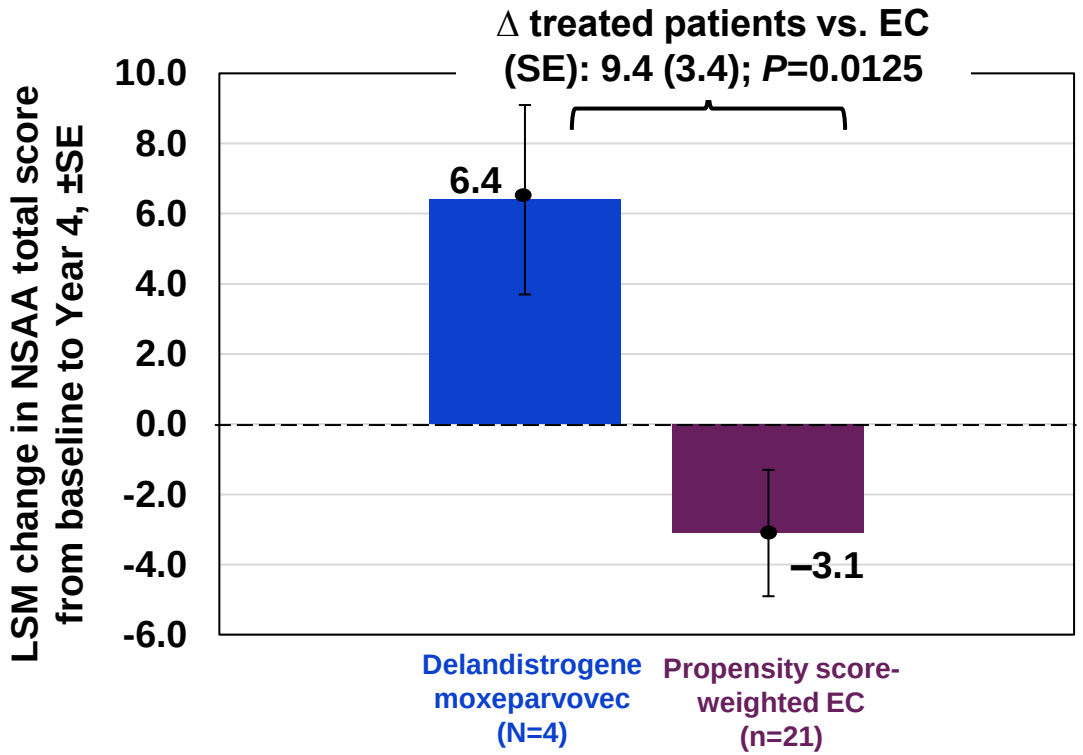
NSAA total score over 4 years after treatment with delandistrogene moxeparvovec versus propensity score-weighted EC cohort

NSAA total score over 4 years in treated patients vs. EC (unadjusted mean)



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 vs. EC (least-squares mean [LSM])



Delandistrogene moxeparvovec (N=4) Propensity score-weighted EC (n=21)

*NSAA change from baseline to 4 years in treated patients versus EC calculated using unadjusted means.
EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error.

Study 101 conclusions

Safety summary

No new safety signals; safety data are consistent with the wider delandistrogene moxeparvovec clinical trial programme

Treatment-related safety events in Study 101 mostly occurred in the first 90 days post-infusion, and all resolved

Reinforced an overall long-term acceptable safety profile

Functional outcomes summary

NSAA showed long-term overall improvements in motor function from baseline that were maintained over 4 years, which demonstrated a durable response and provided evidence of stabilisation of function

- NSAA improvements were generally accompanied by improvement in TFTs over 4 years

In a post hoc analysis, there was a significant difference in NSAA total score in treated patients relative to EC patients (LSM Δ=9.4 [SE ±3.4; *P*=0.0125]); this difference is clinically meaningful

- Four-year data reinforce that delandistrogene moxeparvovec is well tolerated
- 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; EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; TFT, timed function test.