One-year data from ENDEAVOR, a Phase 1b trial of delandistrogene moxeparvovec in patients with DMD

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Acknowledgments and disclosures

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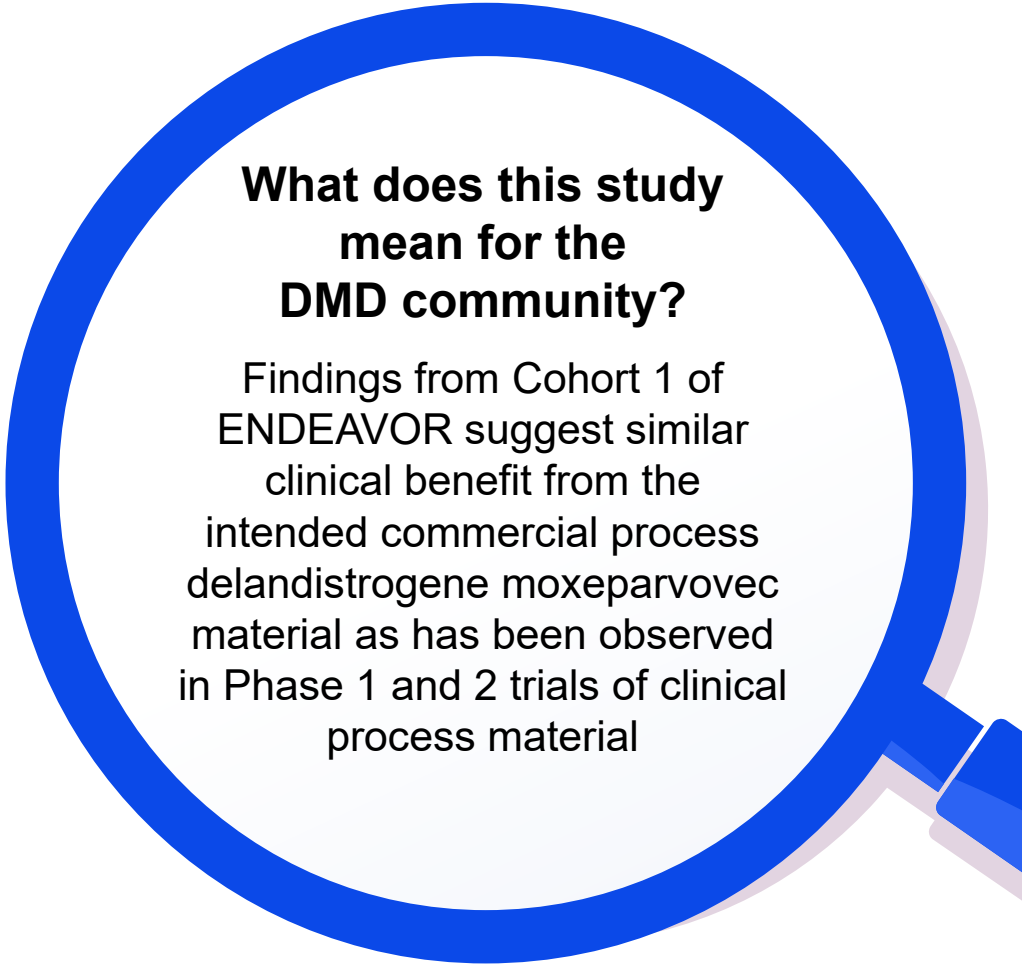
- These data are an encore of data first presented by CM Zaidman at 17th International Congress on Neuromuscular Diseases (ICNMD) 2022

Disclosures

- CMP 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 a principal investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC Therapeutics, Pfizer, Sarepta Therapeutics and Scholar Rock
- CMZ receives research support from and serves on an advisory board for Biogen, was a paid consultant for Optum, and has received research support from Novartis and speaker and consultant fees as well as support for attending meetings from Sarepta Therapeutics
- CMM served as a consultant on clinical trials of DMD for Astellas, Avidity Biosciences, Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Entrada Therapeutics, Epirium Bio (formerly Cardero Therapeutics), FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, and Sarepta Therapeutics. He reports honoraria for presentations from PTC Therapeutics, Sarepta Therapeutics, Solid Biosciences, Santhera Pharmaceuticals, Capricor Therapeutics, and Catabasis. He has received compensation for participation on advisory boards from PTC Therapeutics, Sarepta Therapeutics, Avidity Biosciences, Edgewise Therapeutics and Santhera Pharmaceuticals. He has received research support for clinical trials from Capricor Therapeutics, Catabasis, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics, and reports grants from the U.S. Department of Defense, U.S. National Institutes of Health (NINDS), Parent Project Muscular Dystrophy and the National Institute on Disability, Independent Living, and Rehabilitation Research
- SM, SW, ED, SL, JM, DAG, and RAP are employees of Sarepta Therapeutics and may own stocks or have stock options
- MG and CW are employees of F. Hoffmann-La Roche Ltd. and have nothing to disclose
- CR is an employee of Roche Products Ltd and holds stock in F. Hoffman-La Roche Products Ltd
- 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
- 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

Objectives and overview

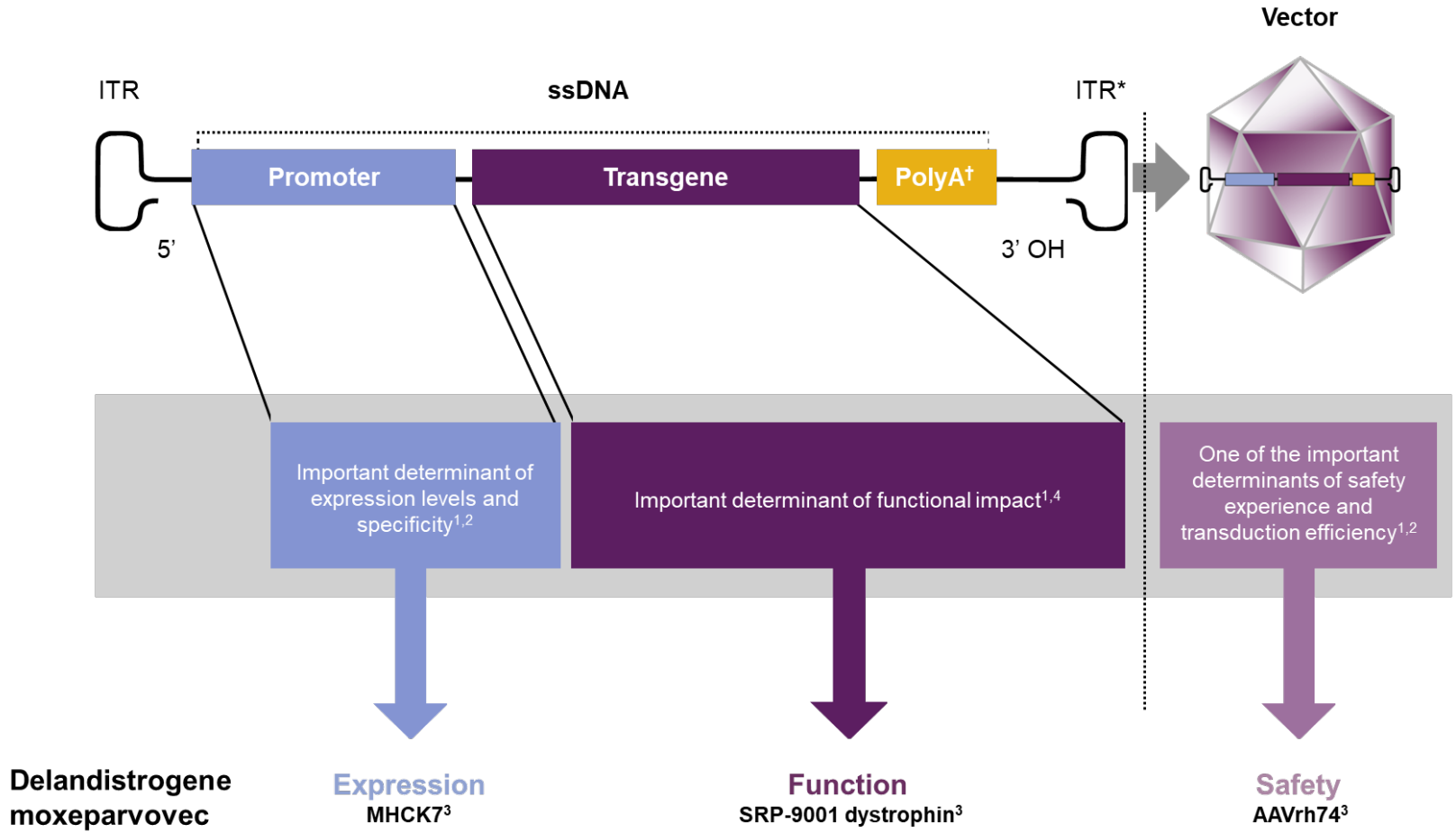
- ENDEAVOR (NCT04626674)[1] is an open-label, Phase 1b study with a primary purpose to assess the expression and safety of intended commercial process delandistrogene moxeparvovec (SRP-9001) material in patients with DMD*
- We present safety, 1-year functional, and 12-week expression data from Cohort 1 of ENDEAVOR
  - A rigorous, well-matched, propensity-score-weighted EC cohort was developed as a pre-specified analysis for comparison with Cohort 1, prior to interim data extraction



*ENDEAVOR used a vector from a different source compared with prior delandistrogene moxeparvovec clinical trials.
DMD, Duchenne muscular dystrophy; EC, external control.
1. ClinicalTrials.gov. NCT04626674 (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, hydroxide; 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

- ENDEAVOR is a two-part, open-label, Phase 1b study assessing the expression and safety of intended commercial process delandistrogene moxeparvovec material in five cohorts of male patients with DMD

Study design: Single IV infusion dose of 1.33×10^{14} vg/kg* of intended commercial process delandistrogene moxeparvovec material

Cohort 1† (ambulatory, ≥4 to <8 years old)

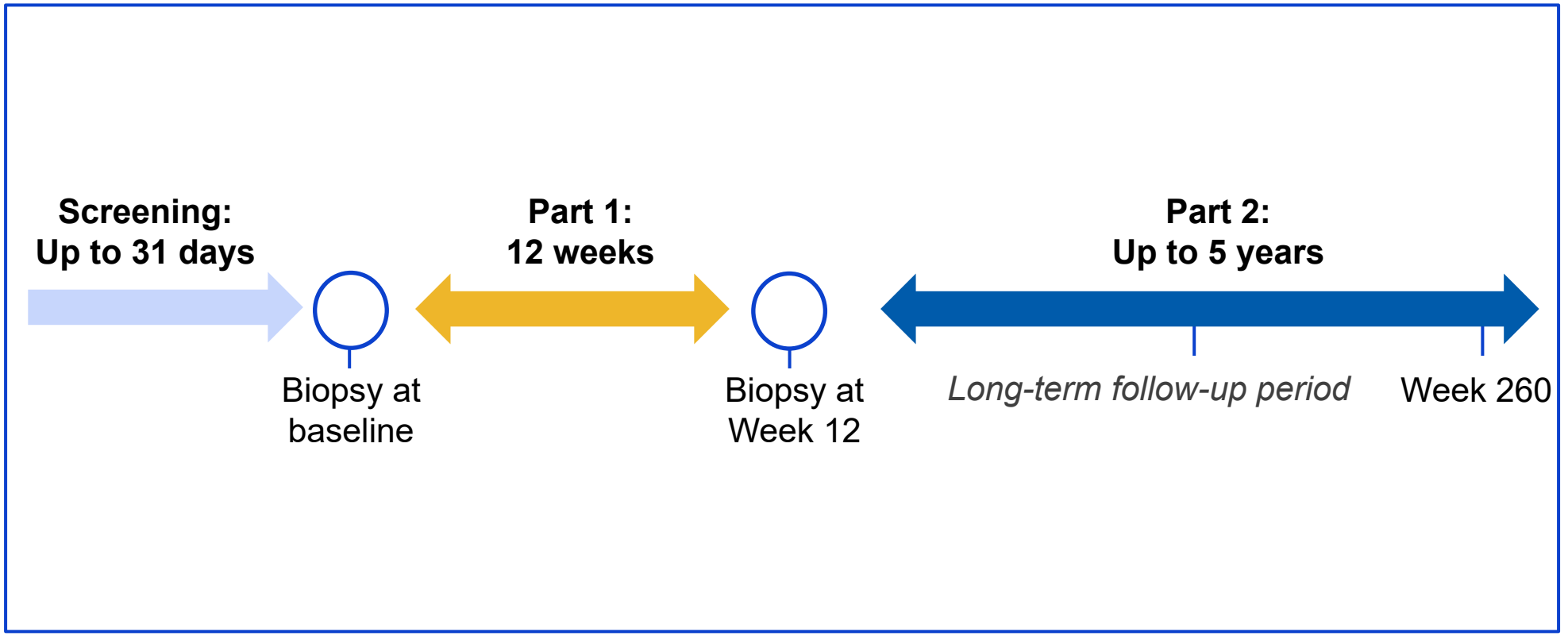
Cohort 2† (ambulatory, ≥8 to <18 years old)

Cohort 3† (non-ambulatory)

Cohort 4† (ambulatory, ≥3 to <4 years old)

Cohort 5a† (ambulatory, ≥4 to <9 years old)

Cohort 5b† (non-ambulatory)



*Linear qPCR. †Only 1-year data for Cohort 1 are shown in this presentation; 1-year data for other cohorts are not yet available; genetic mutation criteria varied by cohort.
DMD, Duchenne muscular dystrophy; IV, intravenous; qPCR, quantitative polymerase chain reaction.

Endpoints

Primary endpoint

- **Change from baseline in quantity of SRP-9001 dystrophin protein expression at Week 12, as quantified by WB**

Secondary endpoints:

- Safety, assessed by the incidence of TEAEs and SAEs, or clinically significant abnormalities in laboratory or vital signs
- Change from baseline in quantity of muscle fiber-localized SRP-9001 dystrophin protein expression, as measured by IF fiber intensity and PDPF at Week 12

Exploratory endpoints:

- NSAA total score (Cohorts 1, 2, and 4)
- TFTs (100MWR, time to ascend 4 steps, time to rise from the floor [supine to stand], and 10MWR; Cohorts 1, 2, and 4)
- Vector genome copies

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; IF, immunofluorescence; NSAA, North Star Ambulatory Assessment; PDPF, percent dystrophin-positive fibers; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TFT, time function test; WB, western blot.

Propensity-score-weighted EC cohort (n=91*)

EC comparator†
- CINRG/DNHS[1,2] (NCT00468832;[3] n=15)
- FOR-DMD[4] (NCT01603407;[5] n=78)
- Lilly Study (H6D-MC-LVJJ; NCT01865084;[6] n=15)

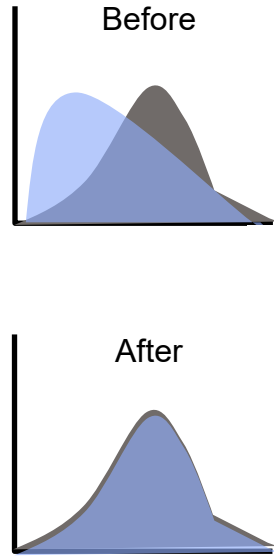
Inclusion Criteria‡
- Age matched at baseline
- NSAA total score ≥13 to ≤30
- Supine to stand ≤10.4 seconds
- 10MWR ≤9.1 seconds
- On stable dose or equivalent of oral corticosteroids for ≥12 weeks pre-baseline§

Propensity score weighting analysis
- Age
- NSAA
- Supine to stand
- 10MWR results

Prognostic factors in DMD that are known to impact function

Ensures maximum comparability between this external cohort and the delandistrogene moxeparvovec groups

Example: Before propensity-score weighting, the ranges are the same but with unequal distribution‖



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

*N=108 before propensity-score weighting. After excluding subjects with non-overlapping propensity scores, n=91. †CINRG was a prospective natural history study of patients with DMD. 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. The Lilly study was a Phase 3, randomized, placebo-controlled trial of tadalafil in patients with DMD. Only placebo patients were included as EC patients for the analysis. ‡Criteria ranges represent the ranges of values measured in the pool of patients treated with delandistrogene moxeparvovec. §Pre-baseline = prior to first functional assessment. ‖Propensity-score weighting involves taking an EC group with similar ages and functions, but unequal distribution, and ensuring overlap after propensity-score weighting. Example ECs before and after propensity-score weighting are shown in the example graphs.

10MWR, 10-meter Walk/Run; 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; NSAA, North Star Ambulatory Assessment.

1. https://cinrgresearch.org/ (Accessed March 2023; 2. Thangarajh M, et al. *PLoS Curr*. 2018; 10:ecurrents.md.4cdeb6970e54034db2bc3dfa54b4d987; 3. ClinicalTrials.gov. NCT00468832 (Accessed March 2023); 4. https://for-dmd.org/en/ (Accessed March 2023); 5. ClinicalTrials.gov. NCT01603407 (Accessed March 2023); 6. ClinicalTrials.gov. NCT01865084 (Accessed March 2023).

Baseline characteristics of Cohort 1

Key inclusion criteria (Cohort 1)

- Ambulatory, male patients, ≥4 to <8 years of age at the time of screening
  - NSAA total score >17 and ≤26
- Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing*
- Stable weekly dose equivalent of oral corticosteroids for at least 12 weeks before screening and the dose is expected to remain constant
- rAAVrh74 antibody titers ≤1:400 (i.e. not elevated)

Characteristic	Total for Cohort 1 (n=20) Mean (SD) Min–max
Age, years†	5.8 (1.1) 4.4–7.9
Height, cm	108.8 (7.7) 94.4–121.0
Dosing weight, kg	21.2 (4.2) 15.2–33.1
Years since DMD diagnosis	2.4 (1.4) 0.9–6.7

*Following the two new treatment-related SAEs observed in Cohort 2 (note: safety data for Cohort 2 are not presented here), inclusion criteria were amended such that mutations between or including exons 1–17 were not eligible. †Age distribution: 11 (55.0%) patients in age category 4–5 years and 9 (45.0%) patients in age category 6–7 years.
DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation.

Safety results from Part 1, Cohort 1

- Safety of the intended commercial process delandistrogene moxeparvovec material was consistent with previous experience with clinical process material*
- No new safety signals were identified in Cohort 1
- In total, 177 TEAEs occurred
  - As seen in previous studies, vomiting was the most common TR-TEAE (55% [11/20] of patients)
- No clinically relevant complement activation was observed
- Two patients experienced a total of two treatment-related SAEs
  - One patient had increased transaminases that required hospitalization for IV corticosteroid treatment
  - One patient experienced vomiting that required IV hydration
- There were no deaths

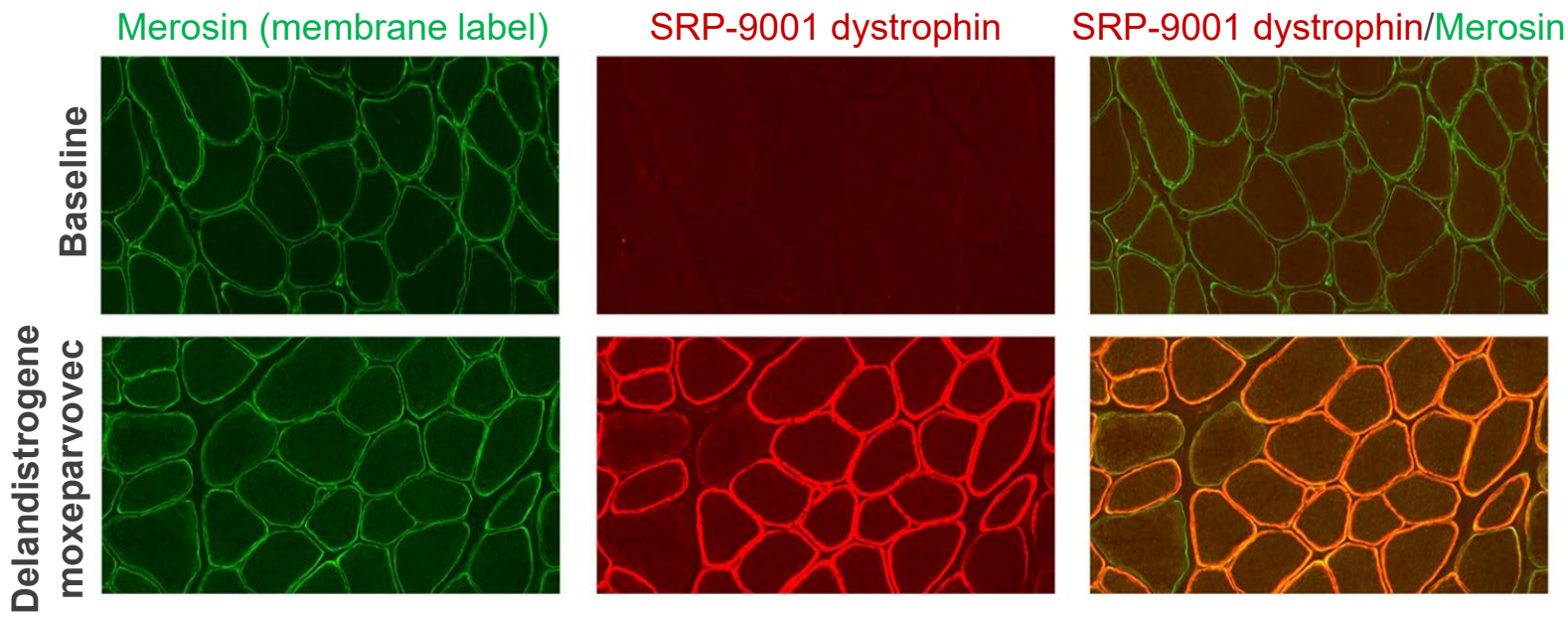
Safety summary	Cohort 1 (n=20)
Total number of AEs, n Patients with at least one AE, n (%)	181 19 (95.0)
Total number of TEAEs, n Patients with at least one TEAE, n (%)	177 19 (95.0)
Total number of TR-TEAEs, n Patients with at least one TR-TEAE, n (%)	105 18 (90.0)
Total number of SAEs, n Patients with at least one: SAE, n (%) Treatment-related SAE, n (%)	2 2 (10.0) 2 (10.0)
Patients with an AE leading to study discontinuation, n	0
Deaths, n	0

*The overall safety profile of delandistrogene moxeparvovec is presented in the MDA 2023 congress poster, “Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD.”
AE, adverse event; DMD, Duchenne muscular dystrophy; IV, intravenous; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TR-TEAE, treatment-related treatment-emergent adverse event.

Example of SRP-9001 dystrophin expression 12 weeks post-infusion

- Treatment with delandistrogene moxeparvovec resulted in robust localization of SRP-9001 dystrophin to the sarcolemma, as shown by IF

SRP-9001 dystrophin expression by IF 12 weeks post-infusion: Example images based on muscle biopsies from the gastrocnemius muscle in Cohort 1*

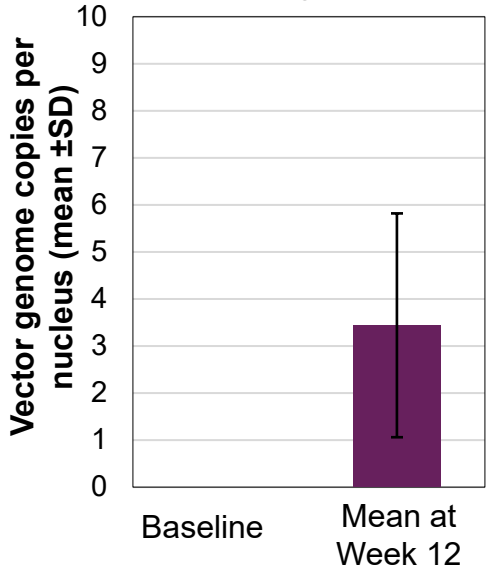


*N=20 patients in Cohort 1; mean PDPF of 56.7% and mean protein intensity at the sarcolemma of 98.4. Images are representative of a participant with 98% PDPF following treatment with delandistrogene moxeparvovec.
IF, immunofluorescence; PDPF, percent dystrophin-positive fibers.

Expression data from Part 1, Cohort 1*

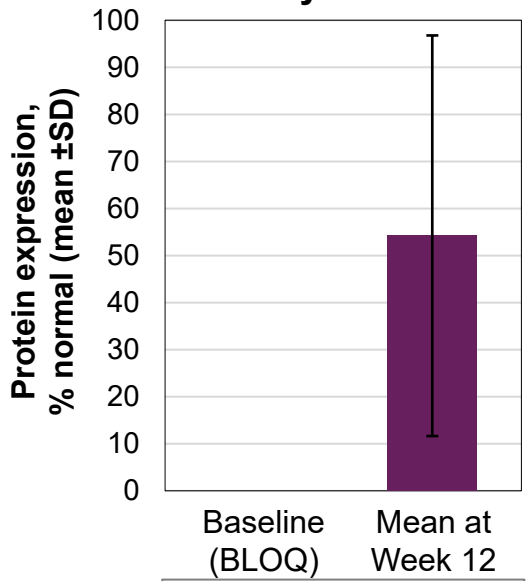
- Treatment with delandistrogene moxeparvovec demonstrated successful transduction of the transgene and expression and localization of the SRP-9001 dystrophin protein product

Vector genome copy number by ddPCR



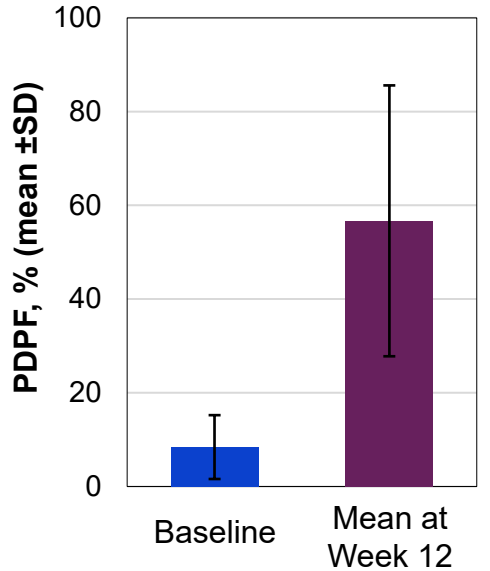
Change from baseline: 3.4±2.4

Protein expression by WB



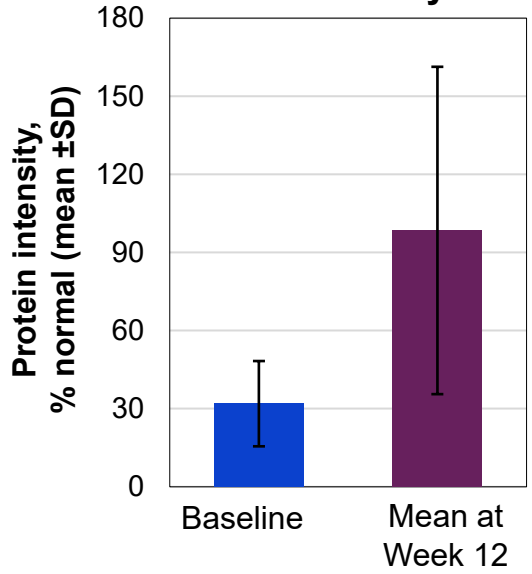
Change from baseline: 54.2±42.6

PDPF by IF



Change from baseline: 48.3±25.4

Protein intensity at the sarcolemma by IF



Change from baseline: 66.5±64.1

*N=20 patients in Cohort 1.
BLOQ, below limit of quantification; IF, immunofluorescence; ddPCR, droplet digital polymerase chain reaction; PDPF, percent dystrophin-positive fibers; SD, standard deviation; WB, western blot.

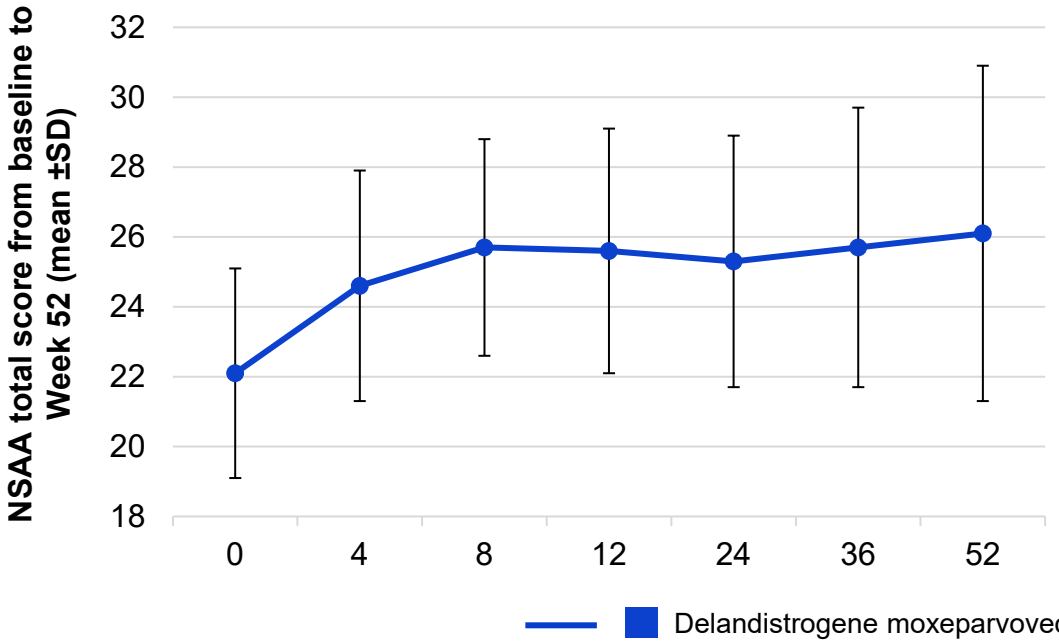
Functional characteristics of Cohort 1 and the EC cohort

Characteristic	Total for Cohort 1 (n=20) Mean (SD) Min–max	Total for EC cohort (n=91) Mean (SD) Min–max
Age, years	5.8 (1.1) 4.4–7.9	6.2 (0.4) 4.2–7.9
NSAA total score	22.1 (3.0) 18–26	21.9 (1.9) 13–30
Supine to stand, seconds	4.2 (1.4) 2.4–8.2	4.2 (0.6) 1.9–9.9
Time of 10MWR, seconds	5.1 (0.8) 3.5–6.7	5.1 (0.4) 3.0–7.5

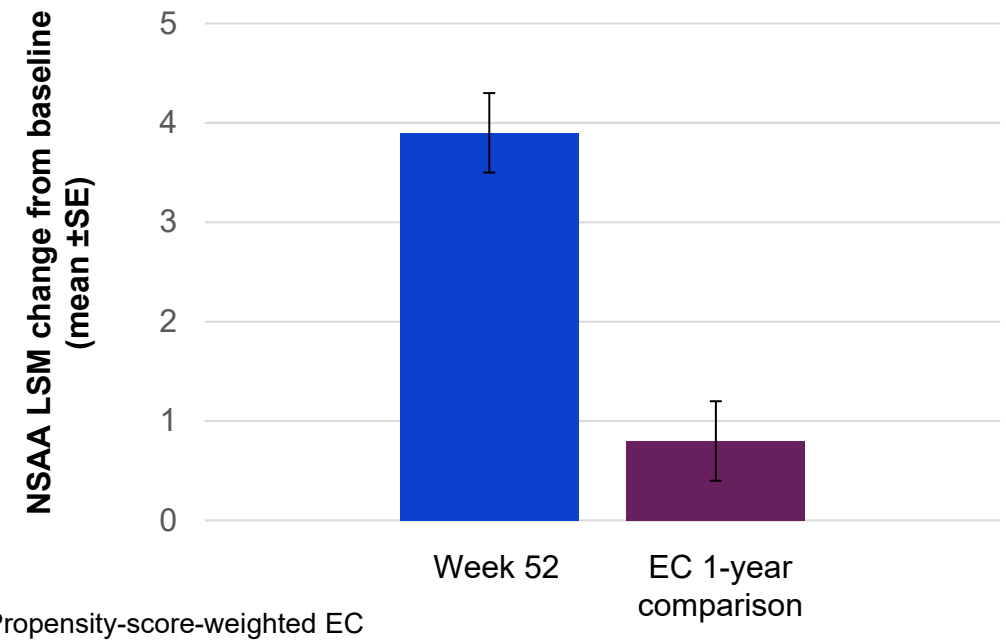
10MWR, 10-meter Walk/Run; EC, external control; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

Functional results: NSAA

Mean change in NSAA total score from baseline to Week 52 (SD): +4.0 (3.5)



LSM change from baseline ±SE of treated patients: 3.9±0.4
LSM change from baseline ±SE of EC: 0.8±0.4
Δ treated patients versus EC: 3.2; P<0.0001



- Changes from baseline in NSAA were measured at Week 52 and compared with a propensity-score-weighted EC
- Treatment with intended commercial process delandistrogene moxeparvovec material led to improvements in motor function

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

Functional results: TFTs

Characteristic	Baseline mean (SD)	Week 52 mean (SD)	Mean change from baseline at Week 52 (SD)
Supine to stand, seconds	4.2 (1.4)	3.7 (2.1)	–0.5 (1.5)
10MWR, seconds	5.1 (0.8)	4.4 (1.0)	–0.8 (0.8)
Time to ascend 4 steps, seconds	3.6 (1.0)	2.8 (1.3)	–0.8 (0.9)
100MWR, seconds	64.1 (20.7)	52.1 (13.7)	–12.0 (18.4)

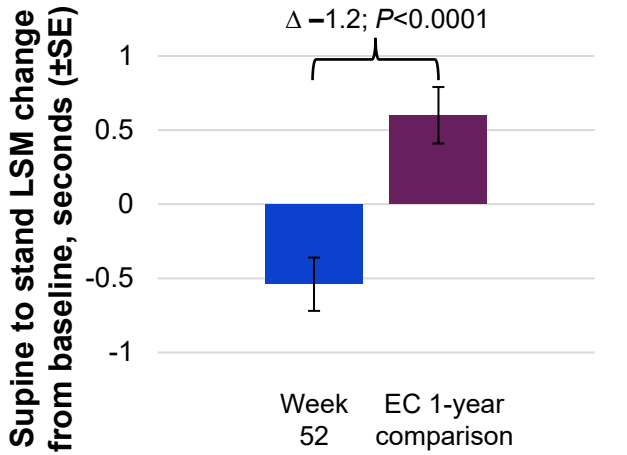
TFTs are measured in seconds. Therefore, decreases in the number of seconds to complete the test following delandistrogene moxeparvovec treatment indicate improvements in motor function

Comparisons with EC data are not available for 100MWR and time to ascend 4 steps

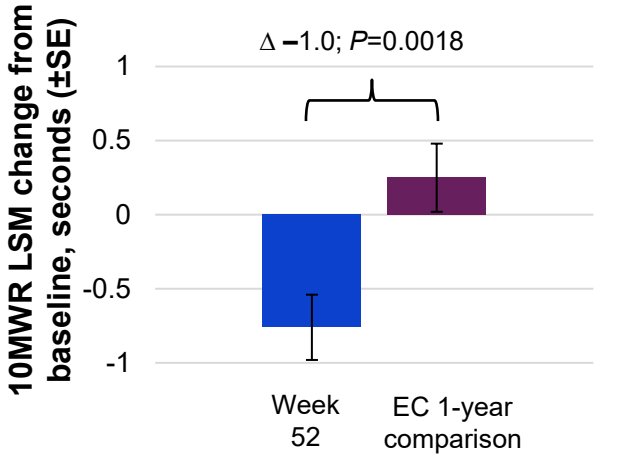
Delandistrogene moxeparvovec

Propensity-score-weighted EC

Supine to stand
LSM change from baseline (±SE)



10MWR
LSM change from baseline (±SE)



10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; EC, external control; LSM, least-squares mean; SD, standard deviation; SE, standard error; TFT, timed function test.

Conclusions

- ENDEAVOR is the first clinical study of delandistrogene moxeparvovec to use intended commercial process delandistrogene moxeparvovec material
- Data from Cohort 1 of ENDEAVOR add to the growing body of evidence supporting improved motor function following treatment with delandistrogene moxeparvovec when compared with an external, propensity-score-weighted EC cohort
- The safety profile of intended commercial process delandistrogene moxeparvovec material in this analysis was consistent with that of previous studies of delandistrogene moxeparvovec clinical process material*

*The overall safety profile of delandistrogene moxeparvovec is presented in the MDA 2023 poster, “Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD.”
DMD, Duchenne muscular dystrophy; EC, external control.