One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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References, abbreviations and acknowledgements ›

Objectives and overview

- Findings from ongoing Phase 1 and Phase 2 trials of delandistrogene moxeparvovec suggest clinical benefit in people with DMD
- ENDEAVOR (NCT04626674) is an open-label Phase 1 study with a primary purpose to assess the expression and safety of commercially representative delandistrogene moxeparvovec material in four different age groups of boys with DMD
- We present 1-year safety and functional data and 12-week expression data following treatment with delandistrogene moxeparvovec

What does this study mean for the DMD community?

ENDEAVOR provides preliminary evidence of the safety and efficacy of commercially representative delandistrogene moxeparvovec material, consistent with previous studies

DMD, Duchenne muscular dystrophy.

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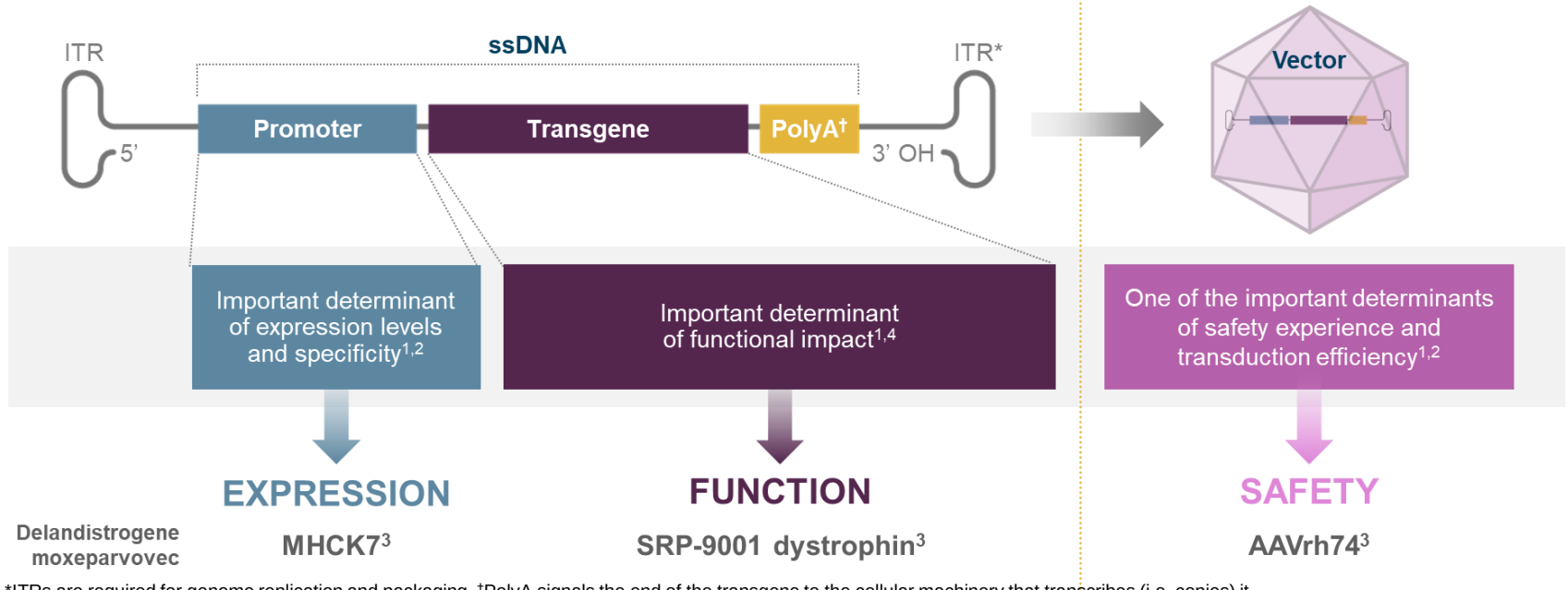
Background

- 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]
- Delandistrogene moxeparvovec is being studied in patients with DMD



*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.

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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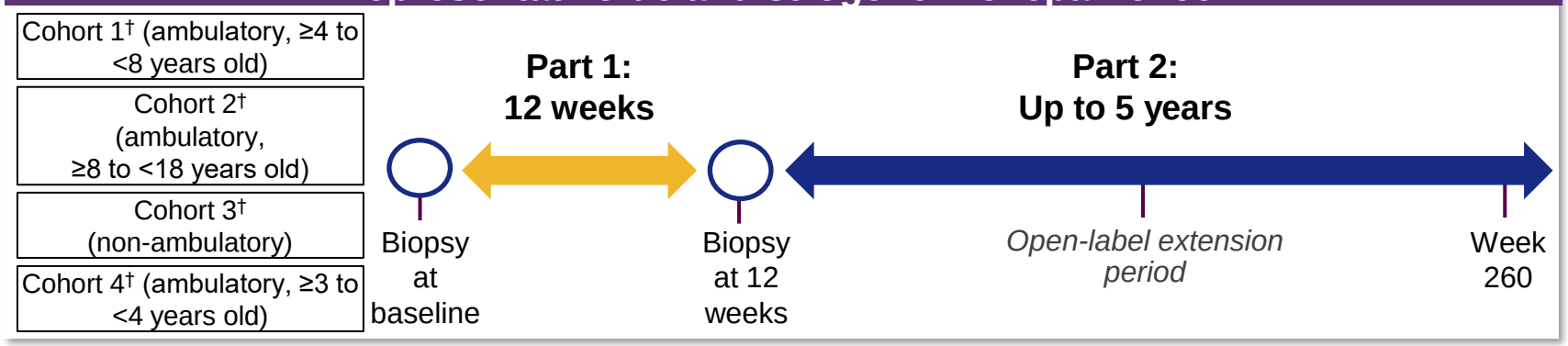
Study design

- ENDEAVOR (NCT04626674)[1] is a two-part, open-label, Phase 1b study assessing the expression and safety of commercially representative delandistrogene moxeparvovec material in four cohorts of boys with DMD

Study design: Single IV infusion dose of 1.33×10^{14} vg/kg* of commercially representative delandistrogene moxeparvovec



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

1. ClinicalTrials.gov. NCT04626674 (Accessed June 2022).

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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Study design[1]

Primary endpoint

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

Key secondary endpoints

- Safety
- Change from baseline in quantity of SRP-9001 dystrophin protein expression, as measured by IF fibre intensity at Week 12
- Change from baseline in quantity of SRP-9001 dystrophin protein expression, as measured by IF percent dystrophin positive fibres at Week 12

Key exploratory endpoints

- NSAA total score (Cohorts 1, 2 and 4)
- Timed function tests (100-metre walk/run, 4-Stair Climb, Time to Rise and 10-metre walk/run; Cohorts 1, 2 and 4)
- Vector genome copies

IF, immunofluorescence; NSAA, North Star Ambulatory Assessment; WB, western blot.

1. ClinicalTrials.gov. NCT04626674 (Accessed June 2022).

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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Propensity-score-weighted external control (EC) cohort pool (N=108*)

The control cohort includes natural history and external clinical trial data from†:

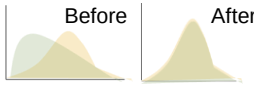
- CINRG/DNHS[1,2] [NCT00468832][3] (n=15)
- FOR-DMD[4] [NCT01603407][5] (n=78)
- Lilly Study (H6D-MC-LVJJ) [NCT01865084][6] (n=15)

Prespecified analysis

Propensity score weighting based on:

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

Example EC before and after propensity weighting§



Based on their ability to predict disease trajectory, the following criteria were used to identify external control patients who were similar to patients enrolled in the delandistrogene moxeparvovec studies:‡

Age
≥4 to ≤8 years old

NSAA score
≥13 and ≤30

Time to Rise
≤10.4 seconds

10-metre Walk/Run
≤9.1 seconds

Stable dose or dose equivalent of oral corticosteroids
for ≥12 weeks pre-baseline¶

*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 external control patients for the analysis. The Lilly study was a Phase 3 randomised, placebo-controlled trial of tadalafil in patients with DMD. Only placebo patients were included as external control patients for the analysis. ‡Criteria ranges represent the ranges of values measured in the pool of patients treated with delandistrogene moxeparvovec. §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. ¶Pre-baseline = prior to first functional assessment.
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, NSAA, North Star Ambulatory Assessment.

1. https://cinrgresearch.org/; 2. Thangarajh M, et al. *PLoS Curr*. 2018; 10: ecurrents.md.4cdeb6970e54034db2bc3dfa54b4d987; 3. https://clinicaltrials.gov/ct2/show/NCT00468832 (Accessed June 2022); 4. https://for-dmd.org/en/ (Accessed June 2022); 5. https://clinicaltrials.gov/ct2/show/NCT01603407 (Accessed June 2022); 6. https://clinicaltrials.gov/ct2/show/NCT01865084 (Accessed June 2022).

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Baseline demographics of Cohort 1

Key inclusion criteria (Cohort 1)

- Ambulatory, male patients ≥4 to <8 years of age at the time of screening
  - NSAA score of >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 titres ≤1:400 (i.e. not elevated)

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

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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Safety results from Part 1, Cohort 1

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 (%) Treatment-related TEAE, n (%)	177 19 (95.0) 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

Safety of the commercially representative delandistrogene moxeparvovec material was consistent with previous experience with delandistrogene moxeparvovec.* No new safety signals were identified in Cohort 1

- In total, 177 TEAEs occurred
  - As seen in previous studies, vomiting was the most common TEAE (55% of patients)
- No clinically relevant complement activation was observed
- A total of two patients experienced two treatment-related SAEs
  - One patient had increased transaminases that required an increase in corticosteroid treatment
  - One patient experienced vomiting that required intravenous hydration
- No deaths were observed

*The overall safety profile for delandistrogene moxeparvovec is presented in ICNMD 2022 poster #eP02.05.05: "Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD."
AE, adverse event; DMD, Duchenne muscular dystrophy; SAE, serious AE; TEAE, treatment-emergent AE.

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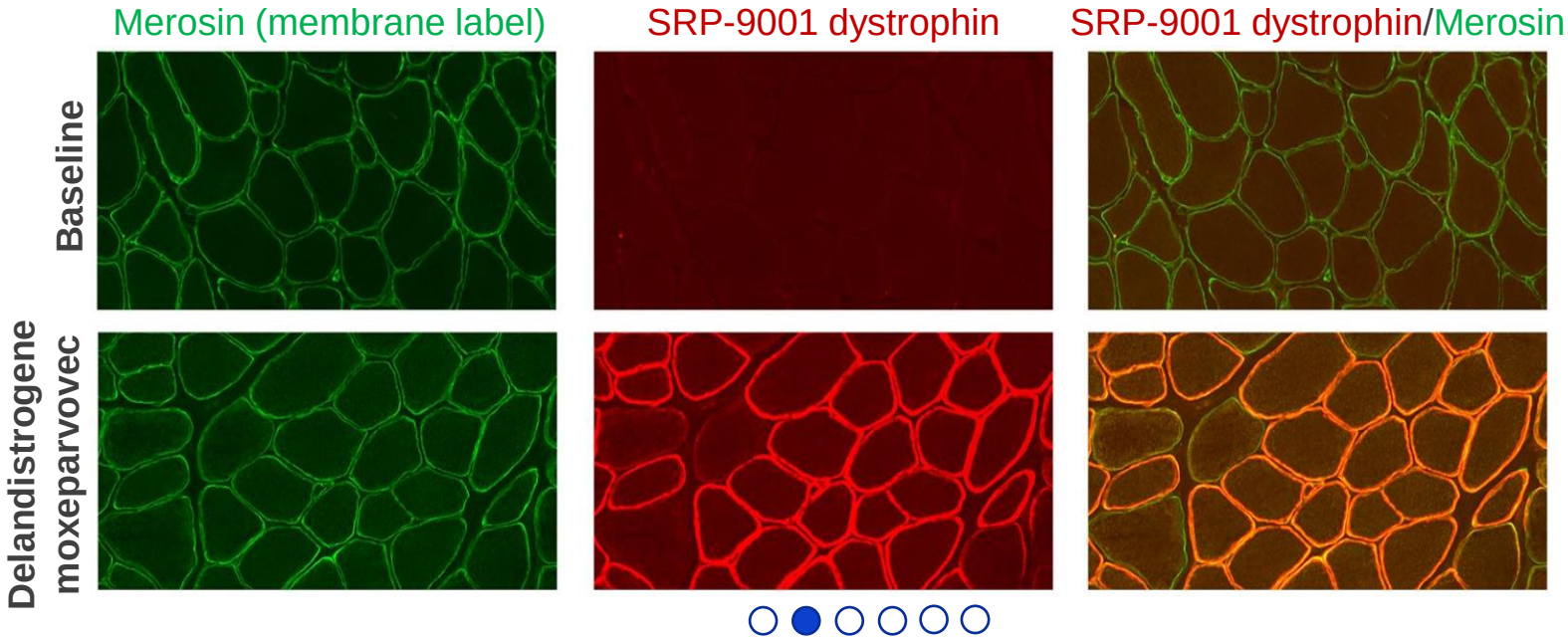
Example of SRP-9001 dystrophin expression 12 weeks post-infusion

- 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.

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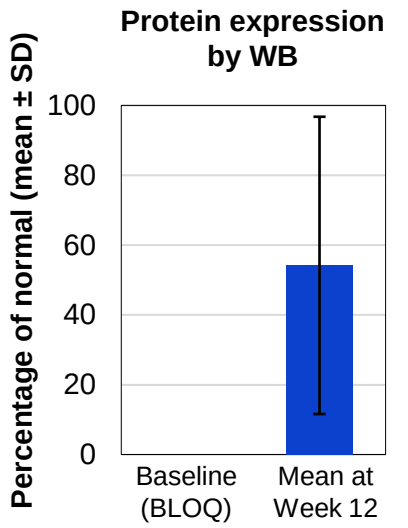
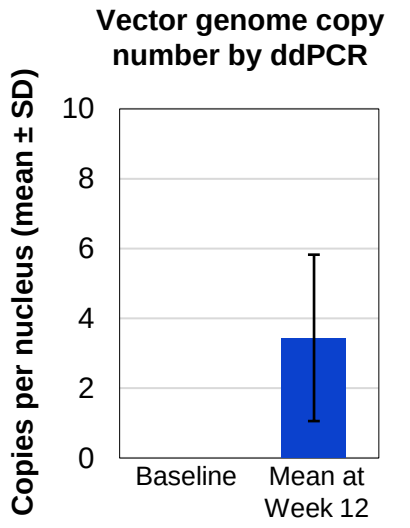
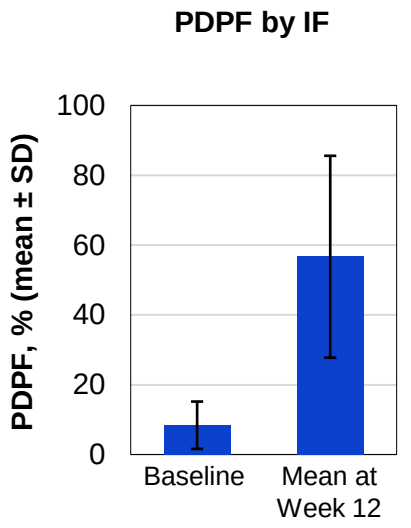
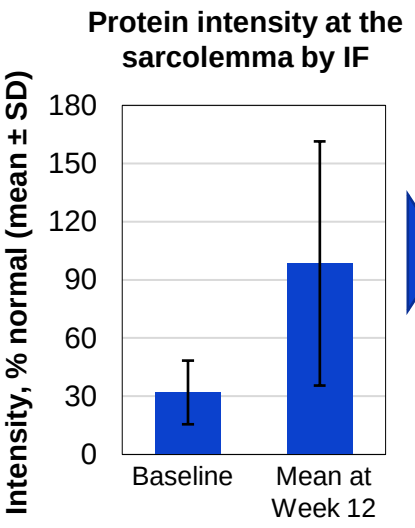
Expression data*

- Demonstration of SRP-9001 dystrophin expression corresponded with vector genome copies, confirming successful delivery of delandistrogene moxeparvovec to target cells









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

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Functional characteristics of Cohort 1 and external control cohort

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

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

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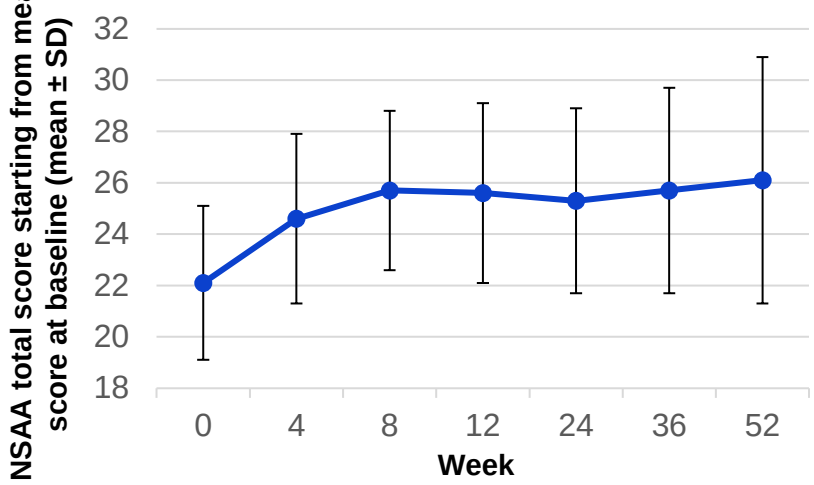
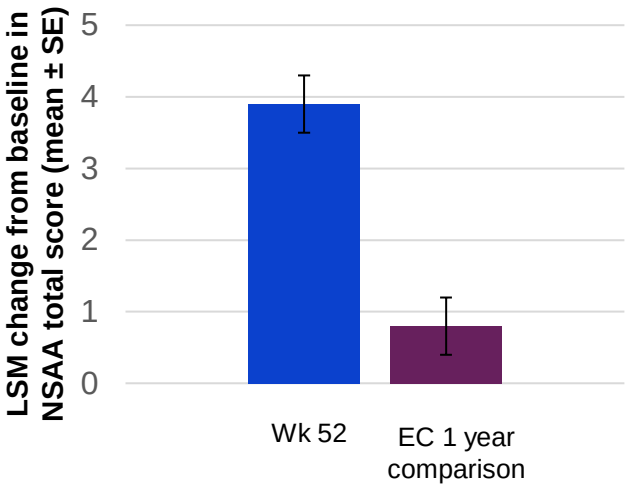
Functional results: NSAA

NSAA total score over 1 year in patients treated with delandistrogene moxeparvovec

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 vs EC: 3.2; P*<0.0001**





Delandistrogene moxeparvovec Propensity-score-weighted EC

- Changes from baseline in NSAA were measured at Week 52 and compared to a propensity-score-weighted EC
- Commercially representative delandistrogene moxeparvovec led to improvements in motor function

EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SE, standard error.
Roche/Sarepta data on file (2022).

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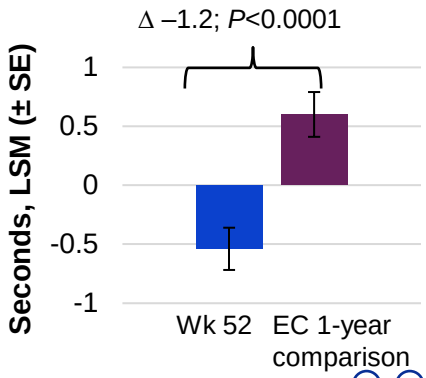
Functional data: Timed function tests

	Baseline mean (SD)	Year 1 mean (SD)	Mean change from baseline at Year 1 (SD)
Time to rise, seconds	4.2 (1.4)	3.7 (2.1)	–0.5 (1.5)
10-metre walk/run, 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)
100-metre walk/run, seconds	64.1 (20.7)	52.1 (13.7)	–12.0 (18.4)

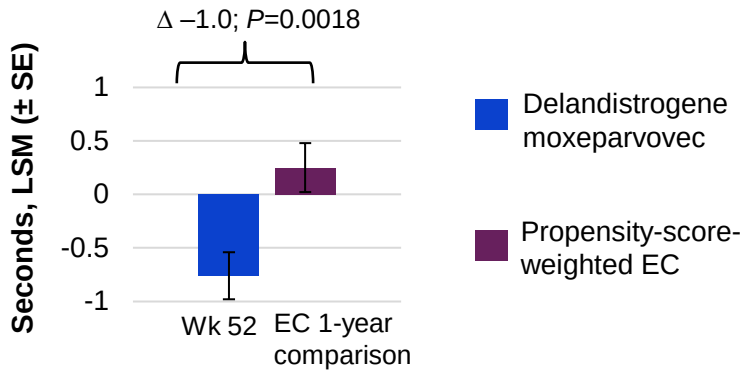
Timed function tests are measured in seconds. Therefore, decreases in the number of seconds to complete the test following delandistrogene moxeparvovec treatment indicate improvements in motor function

Comparisons to EC data are not available for 100-metre walk/run and Time to ascend 4 steps

Time to rise
LSM change from baseline (± SE)



10-metre walk/run
LSM change from baseline (± SE)



EC, external control; LSM, least-squares mean; SD, standard deviation; SE, standard error.

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

C Zaidman,[1] C Proud,[2] C McDonald,[3] S Mason,[4] M Guridi,[5] S Wang,[4] C Reid,[6] E Darton,[4] C Wandel,[5] S Lewis,[4] J Malhotra,[4] DA Griffin,[4,7] RA Potter,[4] LR Rodino-Klapac,[4] JR Mendell[7,8]

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Conclusions

- ENDEAVOR is the first clinical study of delandistrogene moxeparvovec to use commercially representative 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 to an external, propensity-score-weighted control
- The safety profile of commercially representative delandistrogene moxeparvovec material in this analysis was consistent with previous studies of delandistrogene moxeparvovec clinical process material†

*ENDEAVOR used vector from different source than prior delandistrogene moxeparvovec clinical trials. †The overall safety profile for delandistrogene moxeparvovec is presented in ICNMD 2022 poster #eP02.05.05: "Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD."

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Abbreviations

AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; BLOQ, below limit of quantification; CINRG, Cooperative International Neuromuscular Research Group; ddPCR, droplet digital polymerase chain reaction; DMD, Duchenne muscular dystrophy; DNHS, Duchenne Natural History Study; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; IF, immunofluorescence; ITR, inverted terminal repeat; IV, intravenous; MHCK7, myosin-heavy-chain kinase 7; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; OH, hydroxide; PDPF, per cent dystrophin-positive fibres; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAVrh74; SD, standard deviation; SAE, serious AE; ssDNA, single-stranded DNA; TEAE, treatment-emergent AE; WB, western blot.

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Disclosures

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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, Pfizer, Sarepta, and Scholar Rock.

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SM, SW, ED, SL, JM, DAG and RAP are employees of Sarepta Therapeutics and may have stock options.

MG, CR and CW are employees of F. Hoffmann-La Roche Products Ltd and have nothing to disclose.

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