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

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What does this study mean for the DMD community?

- ENDEAVOR (NCT04626674)[1] provides preliminary evidence of the safety and efficacy of commercially representative delandistrogene moxeparvovec (SRP-9001) material, consistent with previous studies.

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 with a propensity-score-weighted EC cohort.
- The safety profile of commercially representative delandistrogene moxeparvovec material in this analysis was consistent with previous studies of delandistrogene moxeparvovec clinical process material.†

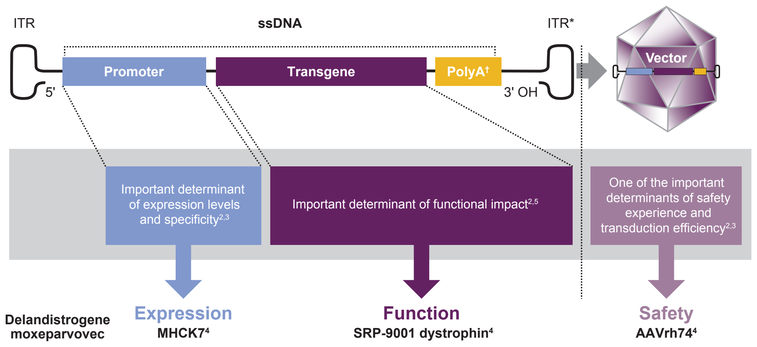
*ENDEAVOR used a vector from a different source to prior delandistrogene moxeparvovec clinical trials. †The overall safety profile of delandistrogene moxeparvovec is presented in the WMS 2022 congress poster, "Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)."

Objective

- Findings from ongoing Phase 1 and Phase 2 trials of delandistrogene moxeparvovec suggest clinical benefit in people with DMD.
- ENDEAVOR is an open-label Phase 1 study with a primary purpose to assess the expression and safety of commercially representative delandistrogene moxeparvovec material in boys with DMD.
- We present 1-year safety and functional data and 12-week expression data from ENDEAVOR.
  - To put the results into context, a post hoc analysis was conducted to compare the functional ENDEAVOR data with data from a propensity-score-weighted EC cohort.

Background

- Delandistrogene moxeparvovec is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin – an engineered, shortened, functional dystrophin protein.[2–4]



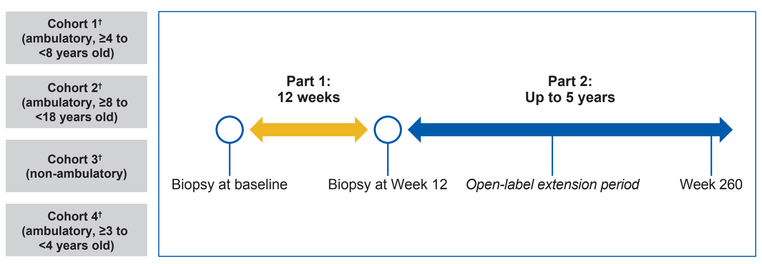
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.

Methods

Study design

- ENDEAVOR 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 1.33x10[14] vg/kg* of commercially representative delandistrogene moxeparvovec material



*Linear qPCR. †Only 1-year data for Cohort 1 are presented in this presentation; 1-year data for other cohorts are not yet available.

Primary endpoint:

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

Secondary endpoints:

- safety
- change from baseline in quantity of SRP-9001 dystrophin protein expression, as measured by IF fibre intensity and IF PDPF at Week 12.

Exploratory endpoints:

- NSAA total score (Cohorts 1, 2 and 4)
- TFTs (100MWR, 4-stair Climb, TTR and 10MWR; Cohorts 1, 2 and 4)
- vector genome copies.

Methods (Contd.)

EC cohort pool (N=108*)

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

- CINRG/DNHS[6,7] (NCT00468832;[8] n=15)
- FOR-DMD[9] (NCT01603407;[10] n=78)
- Lilly study (H6D-MC-LVJJ; NCT01865084;[11] n=15).

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

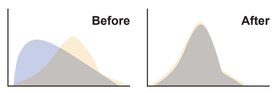
- **Age** ≥4 to ≤8 years old
- **NSAA score** ≥13 and ≤30
- **TTR** ≤10.4 seconds
- **10MWR** ≤9.1 seconds
- **Stable dose or dose equivalent of oral corticosteroids** for ≥12 weeks pre-baseline§

Pre-specified analysis

Propensity-score weighting was performed to ensure maximum comparability between the EC cohort and the delandistrogene moxeparvovec groups, based on:

- age
- NSAA
- TTR
- 10MWR.

Example EC before and after propensity-score weighting‖



*N=108 before propensity-score weighting. After excluding EC 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, randomised, 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 age and function, but unequal distribution, and ensuring overlap after propensity-score weighting. Example EC before and after propensity-score weighting is shown in the example graphs.

Results

Baseline demographics

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

- After propensity-score weighting, the baseline functional characteristics of Cohort 1 and the EC cohort were well matched (see supplementary material).

*Age distribution: 11 (55.0%) patients in age category 4–5 years and 9 (45.0%) patients in age category 6–7 years.

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 (%)	117 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

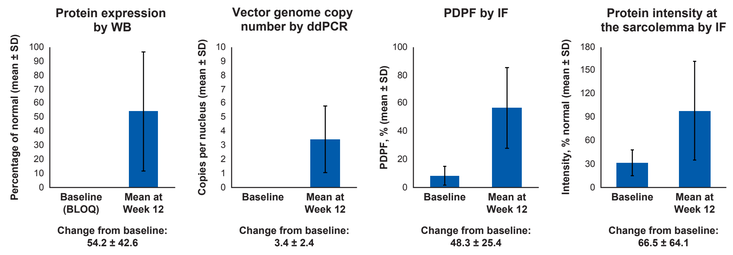
Safety of the commercially representative delandistrogene moxeparvovec material was consistent with previous experience with delandistrogene moxeparvovec.* No new safety signals were identified in Cohort 1.

- 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 IV hydration.
- No deaths were observed.

*The overall safety profile of delandistrogene moxeparvovec is presented in the WMS 2022 congress poster, "Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)."

Results (Contd.)

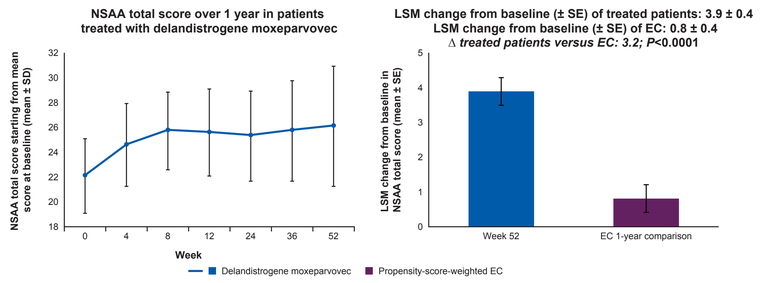
Expression data from Part 1, Cohort 1*



- 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.

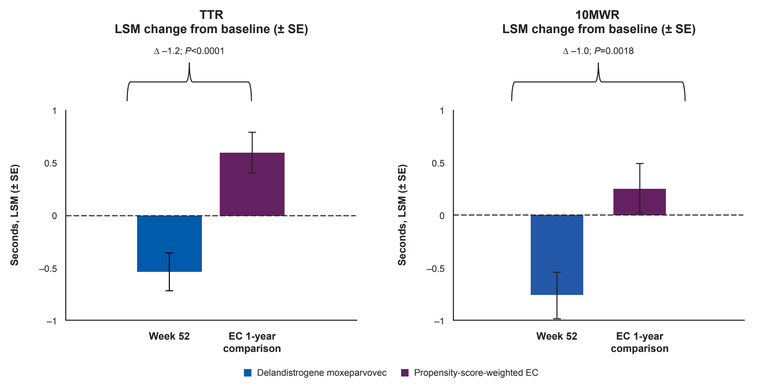
Functional results: NSAA



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

Functional results: TFTs

	Baseline mean (SD)	Year 1 mean (SD)	Mean change from baseline to Year 1 (SD)
TTR, 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)
4-stair Climb, 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 the 100MWR and 4-stair Climb.

Acknowledgements and disclosures

The authors would like to thank the patients and their families for their participation in this study, as well as the investigators and trial staff involved in ENDEAVOR. This study was sponsored by Sarepta Therapeutics, Inc., Cambridge, MA, USA and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland. CZ 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 fees from 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, Pfizer, Sarepta Therapeutics, and Scholar Rock. CM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other from Capricor, Catabasis, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. 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 Ltd and have nothing to disclose. 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. LRRK 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. 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) and was funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Abbreviations

10MWR, 10-metre walk/run; 100MWR, 100-metre walk/run; 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; LSM, least squares mean; MHCK, myosin-heavy-chain kinase; NSAA, North Star Ambulatory Assessment; OH, hydroxide; PolyA, polyadenylation; PDPF, percent dystrophin-positive fibres; qPCR, quantitative polymerase chain reaction; SAE, serious AE; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TEAE, treatment-emergent AE; TFT, timed function test; TTR, Time to Rise; vg, vector genome; WB, western blot.

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Presented at the 27th International Annual Congress of the World Muscle Society (WMS), Halifax, Canada, October 11–15, 2022

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Supplementary material

Functional characteristics of Cohort 1 and EC cohort

Functional characteristic	Total for Cohort 1 (N=20) mean (SD)	Total for EC cohort (n=91) mean (SD)
Age, years	5.8 (1.1)	6.2 (0.4)
NSAA total score	22.1 (3.0)	21.9 (1.9)
TTR, seconds	4.2 (1.4)	4.2 (0.6)
10MWR, seconds	5.1 (0.8)	5.1 (0.4)

Abbreviations

10MWR, 10-metre walk/run; EC, external control; NSAA, North Star Ambulatory Assessment; SD, standard deviation; TTR, Time to Rise.