Delandistrogene Moxeparvovec Micro-Dystrophin Expression and Safety in 3–4-year-olds with Duchenne Muscular Dystrophy in ENDEAVOR and ENVOL Studies

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*At the time of the studies (currently employed by Sarepta Therapeutics, Inc.).

Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered, functional form of dystrophin shown to stabilize or slow disease progression in ambulatory patients with DMD[1–4]
- Delandistrogene moxeparvovec is approved in the USA and in other select countries[5–13]
- Delandistrogene moxeparvovec is being assessed in a broad clinical development program in patients of all ages and with various *DMD* pathogenic variants
  - ENDEAVOR is a multi-cohort, open-label, Phase 1b clinical trial (NCT04626674; **Figure 1**);[14] Cohort 4 enrolled ambulatory patients aged ≥3 to <4 years
  - ENVOL is a multi-cohort, open-label, Phase 2 clinical trial (NCT06128564; **Figure 2**);[15] Cohort A enrolled ambulatory patients aged ≥3 to <4 years

Objectives

- We report delandistrogene moxeparvovec transduction efficiency, expression, and sarcolemmal localization, as well as safety outcomes in 3–4-year-old ambulatory patients with DMD from ENDEAVOR Cohort 4 and ENVOL Cohort A

Methods

- Patients were treated with a single IV infusion of 1.33×10^{14} vg/kg (by linear qPCR) of delandistrogene moxeparvovec
- Patients in ENDEAVOR Cohort 4 and ENVOL Cohort A were not receiving corticosteroids at time of screening

Figure 1 *ENDEAVOR study design*

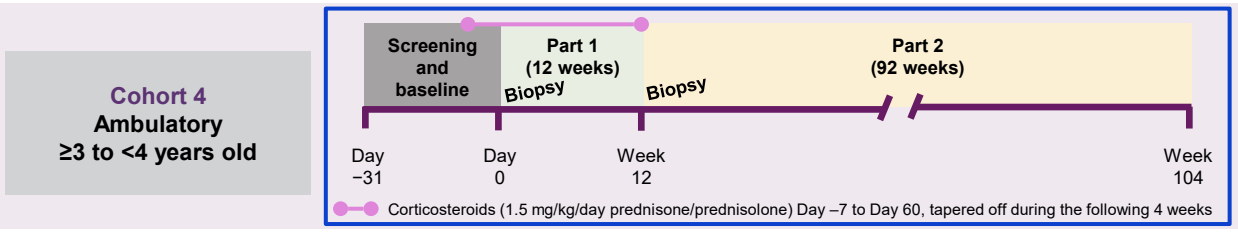
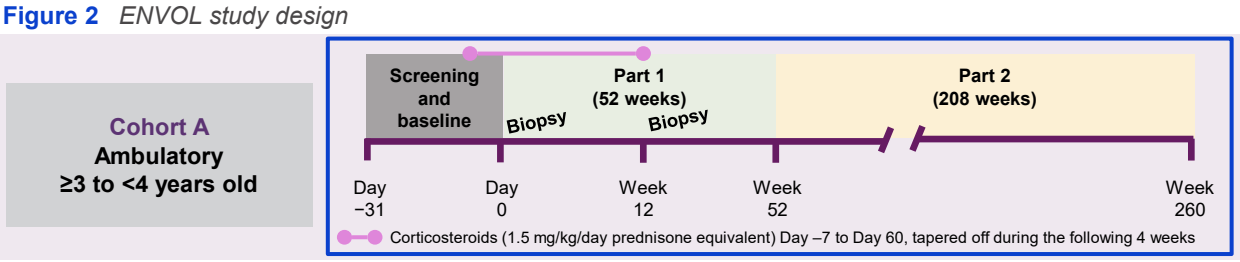


Figure 2 *ENVOL study design*



Results

- At baseline, patients in ENDEAVOR Cohort 4 (N=7) and ENVOL Cohort A (N=10) had a mean (SD) age of 3.5 (0.2) and 3.4 (0.2) years, respectively (**Table 1**)

Table 1 *Baseline characteristics of ambulatory 3–4-year-olds*

Characteristics Mean (SD) (min, max)	ENDEAVOR Cohort 4 (N=7)	ENVOL Cohort A (N=10)
Age, years*	3.5 (0.2) (3.2, 4.0)	3.4 (0.2) (3.1, 3.7)
Dosing weight, kg	15.2 (1.6) (12.5, 16.5)	15.4 (2.2) (12.0, 18.9)
BMI, kg/m^2	17.6 (1.8) (14.8, 20.5)	17.5 (1.7) (15.8, 20.2)
Time since DMD diagnosis, months	15.8 (16.8) (0.7, 38.8)	21.7 (12.3) (3.6, 37.9)
LVEF, %†	63.9 (5.0) (56.4, 72.0)	64.6 (6.9) (56.0, 75.0)

*Age at screening. †Measured by ECHO.

Delandistrogene moxeparvovec transduction efficiency, micro-dystrophin expression, and sarcolemmal localization

Table 2 *Muscle biopsy outcomes in 3–4-year-olds in ENDEAVOR and ENVOL*

Week 12 Mean (SD) (min, max)	ENDEAVOR Cohort 4 (N=7)	ENVOL Cohort A (n=9*)
Vector genome copies, number per nucleus	3.0 (1.3) (1.1, 4.8)	4.8 (2.2) (2.0, 7.7)
Western blot, % control	99.6 (52.0) (46.9, 197.3)	108.9 (56.3) (33.6, 190.7)
PDPF, %†	73.2 (16.0) (54.4, 96.0)	80.5 (19.6) (42.2, 98.3)

*A Week 12 biopsy was not available from one patient. The patient's family consented to biopsy at another timepoint.
†Different methodologies were used to measure PDPF in ENDEAVOR Cohort 4 and ENVOL Cohort A.

- For patients aged 3–4 years, in both ENDEAVOR Cohort 4 and ENVOL Cohort A, Week 12 muscle biopsies showed robust delandistrogene moxeparvovec transduction efficiency, micro-dystrophin expression, and localization to the sarcolemma (**Table 2**)

Safety overview

- Mean (SD) (range) follow-up in ENDEAVOR Cohort 4 (safety data cutoff: July 2, 2024) and ENVOL Cohort A (safety data cutoff: October 21, 2024) was 105.9 (2.6) (101.2 to 110.1) and 20.8 (10.7) (12.0 to 46.7) weeks, respectively
- Most TR-TEAEs were mild to moderate in severity; there were no TR-SAEs, treatment-related deaths, or study discontinuations due to AEs (**Tables 3 and 4**)
- The overall delandistrogene moxeparvovec safety profile is manageable with appropriate monitoring and treatment of AEs, which typically occur within 90 days post-infusion
  - Outside of the ENDEAVOR and ENVOL trials, to date, there have been two treatment-related deaths due to acute liver failure approximately 3 months post-infusion in non-ambulatory patients (one in the ENVISION trial and one in the commercial setting) at 15 and 16 years of age and in the advanced stage of DMD (Data on file)

Table 3 *TR-TEAEs following delandistrogene moxeparvovec infusion*

TR-TEAEs	ENDEAVOR Cohort 4 (N=7)	ENVOL Cohort A (N=10)	TR-TEAEs	ENDEAVOR Cohort 4 (N=7)	ENVOL Cohort A (N=10)
	Patients, n (%)			Patients, n (%)	
Vomiting	3 (42.9)	4 (40.0)	Aggression	-	1 (10.0)
Decreased appetite	3 (42.9)	2 (20.0)	Cough	-	1 (10.0)
Fatigue	-	1 (10.0)	Flushing	-	1 (10.0)
Diarrhea	1 (14.3)	-	Hypersensitivity	-	1 (10.0)
Gastric dilation	1 (14.3)	-	Hypophagia	-	1 (10.0)
Lethargy	1 (14.3)	-	Nausea	-	1 (10.0)
Hepatotoxicity	-	1 (10.0)*	Swelling face	-	1 (10.0)
Hepatic enzyme increased or GLDH increased or LFT increased	3 (42.9)	2 (20.0)			

*This event of hepatotoxicity in ENVOL qualified as an AESI of hepatotoxicity (GGT or GLDH >8x ULN, grade 3 and severe) and was managed with IV methylprednisolone and tacrolimus. This patient was steroid-naïve at screening and received 1.0 mg/kg of prophylactic corticosteroids instead of 1.5 mg/kg per the study protocol from baseline to Week 2.

Table 4 *Safety overview in 3–4-year-olds in ENDEAVOR and ENVOL*

Event	ENDEAVOR Cohort 4 (N=7)		ENVOL Cohort A (N=10)	
	Patients n (%)	Events n	Patients n (%)	Events n
TR-TEAEs	6 (85.7)	21	6 (60.0)	23
TR-SAEs	0 (0)	0	0 (0)	0
Treatment-related deaths	0 (0)	0	0 (0)	0
Study discontinuations due to AEs	0 (0)	0	0 (0)	0

Conclusions

- In the 3–4-year-old patient population, robust delandistrogene moxeparvovec transduction, micro-dystrophin expression, and sarcolemmal localization were observed 12 weeks post-delandistrogene moxeparvovec infusion
- Higher overall mean and higher minimum delandistrogene moxeparvovec micro-dystrophin expression were observed in the 3–4-year-old population compared with previously observed results in ambulatory patients ≥5 years of age and non-ambulatory patient populations[16,17]
- Safety was manageable with appropriate monitoring, with no new signals, and was consistent with the known safety profile of delandistrogene moxeparvovec in other age groups of ambulatory patients (≥4-year-olds)
- Additional cohorts in ENDEAVOR and ENVOL will further evaluate the impact of early screening and treatment on outcomes for patients aged <4 years[14,15]

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Abbreviations

AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; DMD, Duchenne muscular dystrophy; ECHO, echocardiogram; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; IV, intravenous; LFT, liver function test; LVEF, left ventricular ejection fraction; PDPF, percent dystrophin-positive fibers; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; ULN, upper limit of normal.

References

1. Mendell JR, et al. Presented at MDA 2024; Poster #M164; **2.** Asher DR, et al. *Expert Opin Biol Ther*. 2020; 20:263–274; **3.** Zheng C and Baum BJ. *Methods Mol Biol*. 2008; 434:205–219; **4.** Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131; **5.** US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information. https://www.fda.gov/media/169679/download (Accessed October 2025); **6.** Qatar Ministry of Public Health. https://www.moph.gov.qa/english/OurServices/advancedsearch/Pages/servicesdetails.aspx?serviceId=234 (Accessed October 2025); **7.** UAE Ministry of Health & Prevention. https://mohap.gov.ae/en/services/registered-medical-product-directory (Accessed October 2025); **8.** Kuwait Ministry of Health. https://e.gov.kw/sites/kgoenglish/Pages/eServices/MOH/DrugFoodSupplementPrices.aspx (Accessed October 2025); **9.** National Health Regulatory Authority Bahrain. https://www.nhra.bh/Departments/PPR/ (Accessed October 2025); **10.** Oman Ministry of Health. https://www.moh.gov.om/en/hospitals-directorates/directorates-and-centers-at-hq/drug-safetycenter/#Resources (Accessed October 2025); **11.** Ministry of Health Israel. https://israeldrugs.health.gov.il/#!/byDrug (Accessed October 2025); **12.** Ministry of Health Brazil. https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-aprova-registro-de-primeiro-produto-de-terapia-genica-para-distrofia-muscular-de-duchenne-dmd (Accessed October 2025); **13.** Japan Ministry of Health, Labour and Welfare Update. 13 May 2025. Roche data on file; **14.** ClinicalTrials.gov. NCT04626674 (Accessed October 2025); **15.** ClinicalTrials.gov. NCT06128564 (Accessed October 2025); **16.** Mendell JR, et al. *Nat Med*. 2025; 31:332–341; **17.** Proud C, et al. Presented at WMS 2024; Poster #424P.