Micro-dystrophin expression and safety with delandistrogene moxeparvovec gene therapy for DMD in a broad population: Phase 1b trial (ENDEAVOR)

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†Affiliations are at the time that the ENDEAVOR study started (currently employed by Sarepta Therapeutics, Inc.).

What does this study mean for the DMD community?

- This study provides valuable insights into the transduction, micro-dystrophin expression and safety profile of delandistrogene moxeparvovec in a broad population of patients with DMD, expanding our understanding of how AAV gene therapies can be applied in patients with DMD.

Conclusions

- The results demonstrate delandistrogene moxeparvovec transduction and micro-dystrophin expression, regardless of age, weight or ambulatory status.
- Safety was generally consistent with that previously reported.
  - IMM occurred in two patients with a recurrence of IMM symptoms with additional cardiac involvement in one of the patients following weaning of immunosuppression.
  - The IMM events informed the current contraindication in patients with any deletion in exons 8 and/or exon 9 of the *DMD* gene.
- There were no deaths, study discontinuations due to AEs or clinically significant complement-mediated AEs.
- No clinically significant changes in LVEF were observed over 2 years.

OBJECTIVE

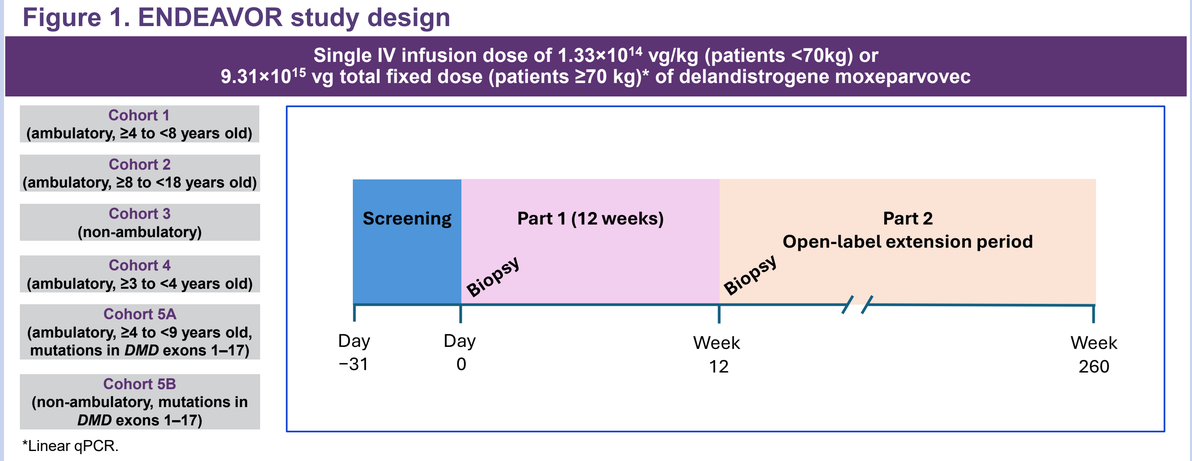
- We report the transduction, expression and safety outcomes of delandistrogene moxeparvovec in patients with DMD across five cohorts from the ENDEAVOR (NCT04626674)[1] study.

BACKGROUND

- DMD is an X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in the absence of functional dystrophin.[2]
- 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 stabilise or slow DMD disease progression;[3–6] it is approved in the US and in other select countries.[7–13]
- ENDEAVOR is a two-part, open-label, Phase 1b study assessing the transduction, expression and safety of delandistrogene moxeparvovec in patients with DMD (**Figure 1**).
- The 1-year results with delandistrogene moxeparvovec in ENDEAVOR Cohort 1 (previously presented) showed robust expression, an acceptable safety profile and stabilisation of motor function, consistent with other delandistrogene moxeparvovec clinical trials (NCT03375164, NCT03769116 and NCT05096221).[2]

METHODS

Figure 1. ENDEAVOR study design



*Linear qPCR.

- **Primary endpoint**: Change in quantity of delandistrogene moxeparvovec micro-dystrophin from baseline to Week 12, as measured by WB.
- **Secondary endpoints:** Safety, assessed by the incidence of TEAEs and SAEs, and change in echocardiogram findings from baseline over 260 weeks (including LVEF).
- **Exploratory endpoint (select):** VGC per nucleus.

RESULTS

- At the time of infusion, ages ranged from 3.24 to 20.23 years and dosing weights ranged from 12.5 to 80.1 kg (**Table 1**).

Table 1. Baseline characteristics

Characteristic	Ambulatory				Non-ambulatory	
	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 4 (N=7)	Cohort 5A (N=6)	Cohort 3 (N=6)	Cohort 5B (N=2)
Age, mean (SD), years; min, max	5.81 (1.14) 4.38, 7.94	10.11 (1.51) 8.00, 12.05	3.48 (0.24) 3.24, 3.95	6.70 (1.43) 4.65, 8.61	15.26 (4.22) 9.86, 20.23	13.43 (1.58) 12.31, 14.55
Dosing weight, mean (SD), kg; min, max	21.15 (4.23) 15.2, 33.1	37.06 (7.64) 28.0, 50.5	15.16 (1.60) 12.5, 16.5	32.12 (10.60) 19.1, 47.4	59.93 (15.17) 36.1, 80.1	51.20 (11.03) 43.4, 59.0
Time since DMD diagnosis, mean (SD), years; min, max	2.36 (1.37) 0.87, 6.74	4.89 (2.01) 2.08, 8.13	1.32 (1.40) 0.06, 3.23	3.27 (1.85) 0.38, 5.17	9.92 (3.96) 5.50, 16.92	8.17 (4.20) 5.21, 11.14
Time since corticosteroid treatment started, mean (SD), years; min, max	0.99 (0.94) 0.10, 4.10	1.89 (1.14) 0.35, 3.38	0.03 (0.05) 0.00, 0.11	1.59 (1.16) 0.25, 3.14	5.70 (5.16) 1.03, 13.98	5.95 (1.09) 5.17, 6.72
Time since loss of ambulation, mean (SD), years; min, max	–	–	–	–	2.54 (2.45) 0.00, 6.85	1.78 (1.38) 0.80, 2.76
Mutation status, n (%) Mutations in exons 1–17 Other	5 (25.0) 15 (75.0)	3 (42.9) 4 (57.1)	0 7 (100)	6 (100) 0	1 (16.7) 5 (83.3)	2 (100) 0
LVEF, mean (range), %	63.75 (53.0–69.0)	58.64 (53.0–62.6)	63.91 (56.4–72.0)	62.53 (55.1–68.0)	55.33 (48.9–62.2)	62.53 (55.1–68.0)

Transduction and delandistrogene moxeparvovec micro-dystrophin expression

- The mean (SD) change from baseline to Week 12 in VGC per nucleus ranged from 1.61 (0.53) to 3.44 (2.38), with transduction in all patients regardless of age, weight or ambulatory status (**Table 2**).
- Pooling across cohorts, the mean (SD) change from baseline to Week 12 in VGC per nucleus was 2.93 (1.96) and 2.67 (0.92) in ambulatory and non-ambulatory patients, respectively.

Table 2. Transduction efficiency and delandistrogene moxeparvovec micro-dystrophin expression at Week 12

	Ambulatory				Non-ambulatory	
	Cohort 1 (N=20) (≥4 to <8 years old)	Cohort 2 (N=7)* (≥8 to <18 years old)	Cohort 4 (N=7) (≥3 to <4 years old)	Cohort 5A (N=6) (≥4 to <9 years old)	Cohort 3 (N=6)	Cohort 5B (N=2)
VGC per nucleus						
Mean (SD)	3.44 (2.38)	1.61 (0.53)	3.00 (1.33)	2.49 (1.34)	2.76 (1.08)	2.41 (0.07)
Median (min, max)	2.72 (0.74, 9.77)	1.57 (0.94, 2.35)	3.52 (1.11, 4.76)	2.36 (0.47, 4.33)	2.79 (1.59, 4.62)	2.41 (2.36, 2.47)
Delandistrogene moxeparvovec micro-dystrophin expression, %						
Mean (SD)	54.21 (42.57)	11.92 (4.21)	99.64 (51.97)	22.82 (21.63)	45.53 (40.59)	23.64 (6.93)
Median (min, max)	50.61 (4.79, 153.92)	10.30 (8.13, 18.63)	83.02 (46.87, 197.25)	18.75 (1.93, 58.88)	37.27 (1.36, 116.28)	23.64 (18.74, 58.88)

*Based on six patients.

- The mean (SD) change in micro-dystrophin expression from baseline to Week 12 ranged from 11.92% (4.21) to 99.64% (51.97) (adjusted for muscle content) and was evident regardless of age, weight or ambulatory status.
- Pooling across cohorts, the mean (SD) change in micro-dystrophin expression from baseline to Week 12 was 51.03% (46.95) and 40.06% (35.86) (adjusted for muscle content) in ambulatory and non-ambulatory patients, respectively.

Limitations

- Patients exhibited a wide range of expression levels as assessed by point muscle biopsies.
  - This wide variability may be more apparent in the averages of small subsets of patients.
  - Of note, expression level observed in an individual's point biopsy may not be representative of their average systemic expression level as there can be variability in expression across an individual's muscle groups and within each muscle.
  - Biopsies were collected from the medial gastrocnemius muscle (Cohorts 1, 4 and 5A) and biceps (Cohorts 2, 3 and 5B).

Safety overview and TR-TEAEs

- See **Supplementary Table 1** for overview of safety.
- Overall, 42 patients (87.5%) experienced 205 TR-TEAEs.
- The most common TR-TEAEs were vomiting (56.3%), nausea (45.8%), glutamate dehydrogenase increased (31.3%) and decreased appetite (27.1%; **Supplementary Table 2**).
- Most TR-TEAEs were mild to moderate in severity; the time of their first occurrence was within 60 days from the infusion (**Figure 2**).
- There were no deaths, study discontinuations due to AEs or clinically significant complement-mediated AEs.

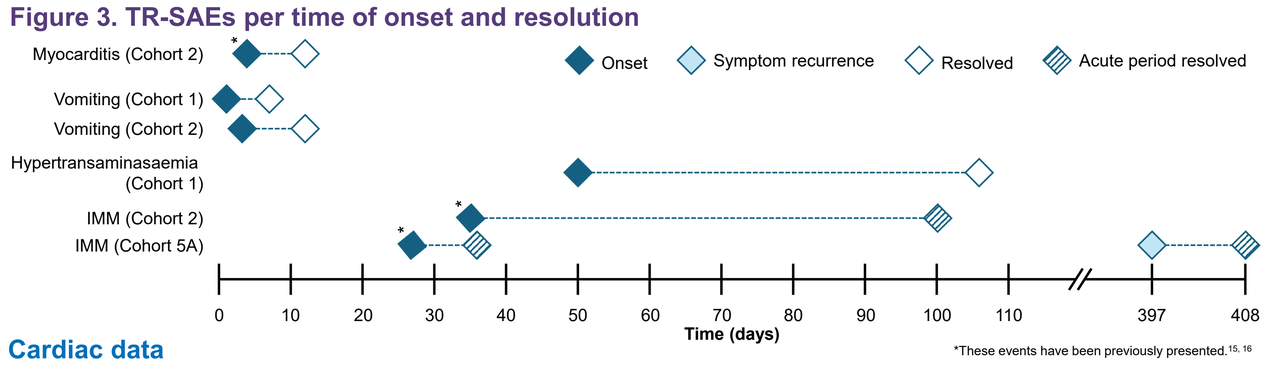
Figure 2. TR-TEAEs by timing of first occurrence

	Day 1 infusion	0–2 weeks	>2 weeks to 60 days	>60 days to 90 days
Vomiting		24 (50.0)	3 (6.3)	0
Nausea		20 (41.7)	2 (4.2)	0
Glutamate dehydrogenase increased		5 (10.4)	7 (14.6)	3 (6.3)
Decreased appetite		12 (25.0)	1 (2.1)	0

TR-SAEs

- One case of myocarditis was reported in a patient treated in Cohort 2 who was initially hospitalised for management of vomiting, during which troponin-I elevation was incidentally detected on Day 4.
  - The patient experienced transient self-limited chest discomfort on Day 6 with no echocardiogram changes.
  - Past medical history included cardiomyopathy with preserved ejection fraction based on cMRI findings of delayed LGE.
  - Troponin-I later returned to baseline levels by Day 17 and myocarditis was reported as resolved on Day 12.
- IMM occurred in two patients with deletions in the *DMD* gene including exons 8 and 9 (one each in Cohorts 2 and 5A).[14]
  - The patient in Cohort 5A exhibited recurrent IMM symptoms on Day 397 with additional cardiac involvement on Day 400 (troponin-I elevation and chest pain) following weaning of immunosuppression 13 months post dosing. Symptoms stabilised approximately 2 weeks later following modification of immunosuppression, while the patient remained haemodynamically stable; cardiac MRI post-discharge showed new LGE with normal LVEF.
  - Only 2 of 6 total patients with deletions in exons 8 and/or 9 in the *DMD* gene developed IMM in ENDEAVOR.
  - Additionally, no other events of IMM occurred in patients with mutations in exons 1–17 in ENDEAVOR (15 out of 17 patients did not develop IMM), including in Cohorts 5A and 5B, which were designed to better understand the risk of IMM.
- See **Supplementary Table 3** for TR-SAEs by cohort.

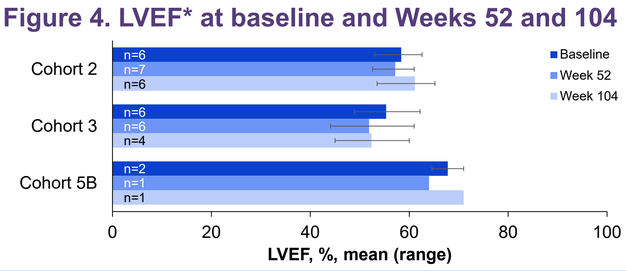
Figure 3. TR-SAEs per time of onset and resolution



*These events have been previously presented.[15, 16]

Cardiac data

Figure 4. LVEF* at baseline and Weeks 52 and 104



- Mean change from baseline suggests no clinically significant changes in LVEF over 2 years.

*Per protocol, LVEF was only evaluated in patients in Cohorts 2, 3, and 5 at Weeks 52 and 104.

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Abbreviations

AAV, adeno-associated virus; AE, adverse event; cMRI, cardiac MRI; DMD, Duchenne muscular dystrophy; IMM, immune-mediated myositis; IV, intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAV rhesus isolate 74; SAE, serious AE; SD, standard deviation; TEAE, treatment-emergent AE; TR-SAE, treatment-related SAE; TR-TEAEs, treatment-related TEAE; WB, western blot; vg, vector genome; VGC, vector genome copies.

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SUPPLEMENTARY INFORMATION

Supplementary Table 1. Overview of safety

Events	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)	Cohort 5 (N=8)	Total (N=48)
Number of AEs	223	91	38	119	79	550
Number of TEAEs	219	86	38	109	75	527
Number of SAEs	2	3	0	0	1	6
Number of TR-TEAEs	106	27	12	21	39	205
Number of TR-SAEs	2	3	0	0	1	6
Patients with any AEs, n (%)	20 (100)	7 (100)	6 (100)	7 (100)	8 (100)	48 (100)
Patients with any TEAEs, n (%)	20 (100)	7 (100)	6 (100)	7 (100)	8 (100)	48 (100)
Patients with any SAEs, n (%)	2 (10.0)	2 (28.6)	0	0	1 (12.5)	5 (10.4)
Patients with any TR-TEAEs, n (%)	18 (90.0)	5 (71.4)	5 (83.3)	6 (85.7)	8 (100.0)	42 (87.5)
Patients with any TR-SAEs, n (%)	2 (10.0)	2 (28.6)	0	0	1 (12.5)	5 (10.4)
Patients with any AEs leading to study discontinuation	0	0	0	0	0	0
Death	0	0	0	0	0	0

Supplementary Table 2. TR-TEAEs occurring in ≥15% of all patients

Events, n (%)	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)	Cohort 5 (N=8)	Total (N=48)
Vomiting	11 (55.0)	3 (42.9)	3 (50.0)	3 (42.9)	7 (87.5)	27 (56.3)
Nausea	8 (40.0)	4 (57.1)	3 (50.0)	0	7 (87.5)	22 (45.8)
Glutamate dehydrogenase increased	9 (45.0)	1 (14.3)	2 (33.3)	1 (14.3)	2 (25.0)	15 (31.3)
Decreased appetite	9 (45.0)	0	1 (16.7)	3 (42.9)	0	13 (27.1)

Supplementary Table 3. TR-SAEs

Events, n (%)	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)	Cohort 5 (N=8)	Total (N=48)
Myocarditis	0	1 (14.3)	0	0	0	1 (2.1)
Vomiting	1 (5.0)	1 (14.3)	0	0	0	2 (4.2)
Hypertransaminasaemia	1 (5.0)	0	0	0	0	1 (2.1)
IMM	0	1 (14.3)	0	0	1 (12.5)*	2 (4.2)

*The patient in Cohort 5A exhibited recurrent IMM symptoms on Day 397 with additional cardiac involvement on Day 400 (troponin-I elevation and chest pain) following weaning of immunosuppression 13 months post dosing. Symptoms stabilised approximately 2 weeks later following modification of immunosuppression, while the patient remained haemodynamically stable; cardiac MRI post-discharge showed new LGE with normal LVEF.

Abbreviations

AE, adverse event; DMD, Duchenne muscular dystrophy; IMM, immune-mediated myositis; LGE, late gadolinium enhancement; SAE, serious AE; TEAE, treatment-emergent AE; TR-SAE, treatment-related SAE; TR-TEAEs, treatment-related TEAE.