Assessment of Cardiac Outcomes in Delandistrogene Moxeparvovec Clinical Trials for Duchenne Muscular Dystrophy

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Disclosure

I have the following conflicts of interest to declare:

- I am an employee of Sarepta Therapeutics, Inc., and own stocks and options in the company

Background

- Cardiorespiratory failure is the most common immediate cause of death in patients with DMD;[1,2] therefore, any disease-modifying DMD therapy needs to be able to target skeletal, respiratory, and cardiac muscles[3]
- Delandistrogene moxeparvovec, an rAAVrh74 vector-based gene transfer therapy approved for the treatment of DMD in the US and other select countries,[4] is designed to drive high expression of micro-dystrophin protein in both skeletal muscle and the heart via the MHCK7 promoter, which contains an α-MHC enhancer that is highly active in the cardiac muscle[5]
- In a mouse model of DMD, treatment with delandistrogene moxeparvovec has been associated with an improvement in cardiac parameters, with no evidence of toxicity[6]
- A more comprehensive characterization of cardiac safety of delandistrogene moxeparvovec in patients is needed

DMD, Duchenne muscular dystrophy; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74.

1. Kieny P, et al. *Ann Phys Rehabil Med.* 2013;56(6):443-54. 2. Soslow JH, et al. *Circ Heart Fail.* 2023;16(8):e010040. 3. Tang A, Yokota T. *Expert Opin Drug Saf.* 2024:1-17. 4. Potter RA, et al. *Sci Rep.* 2025;15(1):4. 5. Mendell JR, et al. *JAMA Neurol.* 2020;77(9):1122-31. 6. Baine S, et al. *Hum Gene Ther.* 2024;35(23-24):978-88.

Methods

Patients

- Data were collected from 4 studies:
  - 101 (NCT03375164; n=4)[1,a]
  - 102 (NCT03769116; n=41)[2,b]
  - ENDEAVOR (NCT04626674, Cohorts 1-5b; n=48)[3,c]
  - EMBARK, Parts 1 and 2 (NCT05096221; n=125)[4,c]
- All studies excluded patients with signs of cardiomyopathy, including an ECHO that indicated LVEF <40%

Cardiac Assessments

- Cardiac specific–monitoring included reporting of cardiac AEs, troponin I measurements, cardiac MRI, and ECHO
  - Troponin I was assessed regularly in ENDEAVOR and EMBARK

Statistical Analysis

- Data are presented using descriptive statistics only

Objective

- To assess pooled **cardiac safety** outcomes from delandistrogene moxeparvovec studies with up to 5 years of follow-up

[a]Cutoff date, June 8, 2023. [b]Cutoff date, September 29, 2023. [c]Cutoff date, January 15, 2024.

AEs, adverse events; ECHO, echocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

1. Mendell JR, et al. *Muscle Nerve.* 2024;69(1):93-8. 2. Mendell JR, et al. *Front Cell Dev Biol.* 2023;11:1167762. 3. Zaidman CM, et al. *Ann Neurol.* 2023;94(5):955-68. 4. Mendell JR, et al. *Nat Med.* 2025;31(1):332-41.

Baseline Characteristics

- Data were collected from 218 patients, of whom 210 (96%) were ambulatory
- At baseline, participants' ages ranged from 3.2 to 20.2 years, and their LVEF values from 48.9% to 78.0%

	Study 101[1] n=4	Study 102[2] n=41	Study 103 (ENDEAVOR)[3] n=48						Study 301 (EMBARK)[4] n=125	
			Cohort 1 n=20	Cohort 2 n=7	Cohort 3 n=6	Cohort 4 n=7	Cohort 5a n=6	Cohort 5b n=2	Treated in Part 1 n=63	Placebo n=62
Ambulatory	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
***DMD* exons affected**	Frame shift (deletion or duplication) or premature stop codon mutation between exons 18 and 58		Pathogenic variant[b] fully contained between exons 18 and 79[c]				Pathogenic variant[b] partially or fully contained between exons 1 and 17[c,d]		Pathogenic variant[b] fully contained between exons 18 and 79[e]	
Age, years, range	4.0 - 6.0	4.3 - 7.9	4.4 - 7.9	8.0 - 12.1	9.9 - 20.2	3.2 - 3.9	4.7 - 8.6	12.3 - 14.6	4.1 - 7.9	4.0 - 8.0
Weight, kg, range	13.7 - 21.4	15.0 - 34.5	15.2 - 33.1	28.0 - 50.5	36.1 - 80.1	12.5 - 16.5	19.1 - 47.4	43.4 - 59.0	13.5 - 38.5	14.4 - 41.6
LVEF%, mean (range)	60.7[f] (57.0 - 65.0)	63.7 (54.5 - 74.0)	63.8 (53.0 - 69.0)	58.6 (53.0 - 62.6)	55.3 (48.9 - 62.2)	63.9 (56.4 - 72.0)	62.5 (55.1 - 68.0)		64.9 (55.0 - 77.0)	64.4 (52.0 - 78.0)
Troponin I, µg/L, mean (range)	-	-	0.02[g] (0 - 0.23)	0.05 (0 - 0.22)	0.13 (0.01 - 0.47)	0.02 (0 - 0.05)	0.02 (0 - 0.11)	0.00 (0 - 0.01)	0.03[h] (0 - 0.59)	0.03[i] (0 - 0.81)
Follow-up, years, mean (range)[j]	5.0 (5.0 - 5.0)	3.5 (2.5 - 4.6)	2.9 (2.7 - 3.0)	2.5 (2.1 - 2.6)	2.5 (2.5 - 2.6)	1.9 (1.8 - 2.0)	0.9 (0.7 - 1.0)	1.0 (0.9 - 1.0)	1.6 (1.3 - 2.1)	1.6 (1.2 - 2.2)

[a]Data in this table do not comprehensively represent all ongoing trials. [b]Expected to lead to absent dystrophin. [c]Initial inclusion criteria allowed for any mutations in *DMD* exons 1 through 79; however, an immune-mediated myositis event in a patient with a large deletion in the exon 1 to 17 region of the *DMD* gene prompted an update to the inclusion criteria. [d]Excludes deletions that fully include exons 9 to 13. [e]Excludes mutations fully contained within exon 45. [f]n=3. [g]n=19. [h]n=62. [i]n=61. [j]Follow-up duration = (date of censoring – infusion date +1)/365.25.

DMD, dystrophin gene; LVEF, left ventricular ejection fraction.

1. Mendell JR, al. *Muscle Nerve.* 2024;69(1):93-8. 2. Mendell JR, et al. *Front Cell Dev Biol.* 2023;11:1167762. 3. Zaidman CM, et al. *Ann Neurol.* 2023;94(5):955-68. 4. Mendell JR, et al. *Nat Med.* 2025;31(1):332-41.

Cardiac Adverse Events

- Two cases of myocarditis were reported by the investigator within days of delandistrogene moxeparvovec infusion; both resolved within 3 weeks, 1 with an addition of another cardiac medication
- Another patient, from ENDEAVOR Cohort 5a, experienced a recurrence of immune-mediated myositis with concurrent cardiac inflammation during immunosuppressant weaning and stabilized with 2 weeks of treatment[1]

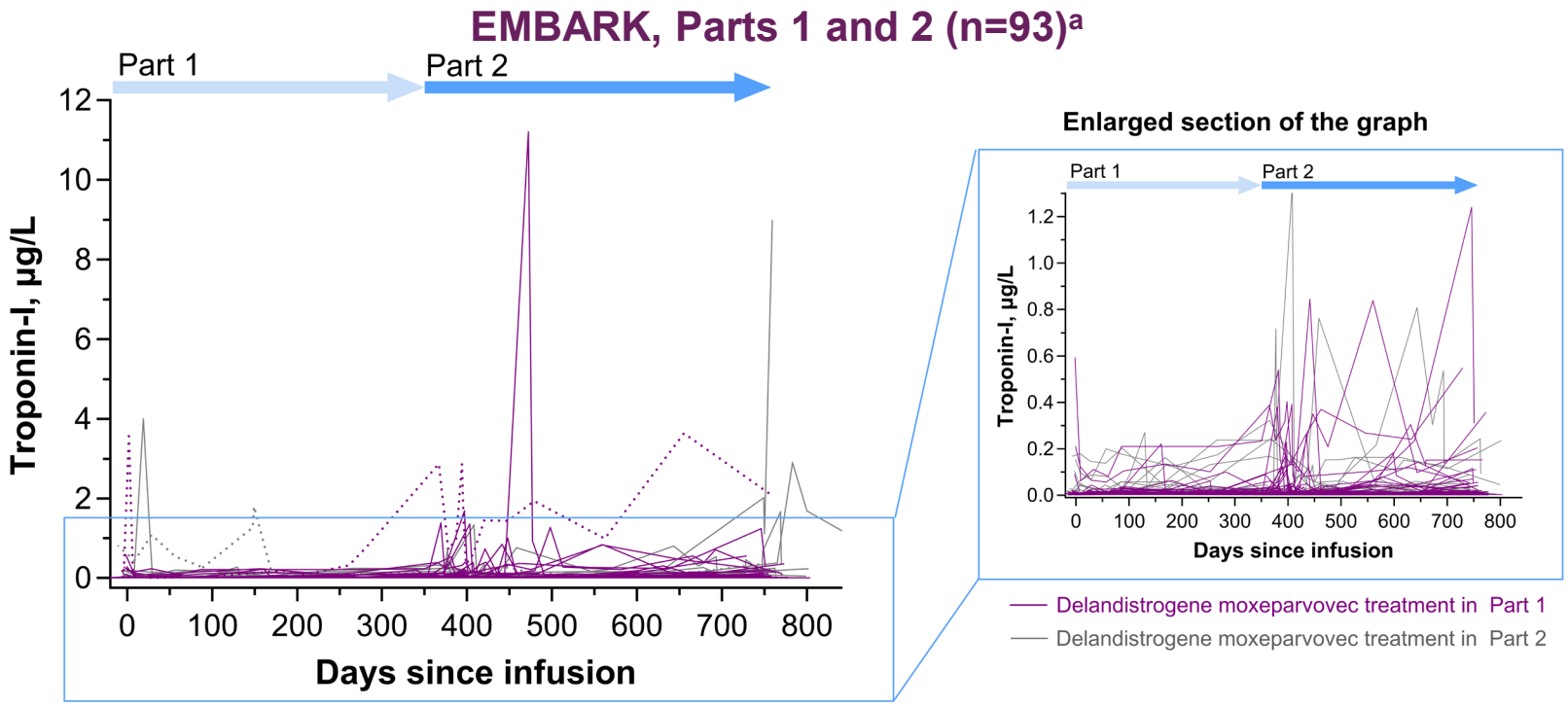
	Patient 1 (ENDEAVOR, Cohort 2)	Patient 2 (EMBARK, Part 1)
Age, years	11	6
Body mass, kg	50.5	20
Medical history	DMD-related cardiomyopathy (LVEF 60%)	Asthma, seasonal allergies
Post-treatment day of onset of myocarditis-related symptoms	Day 3: Nausea, vomiting Day 4: Troponin increase Day 6: Self-limited chest discomfort	Day 1: Fever, nausea, vomiting, episode of shaking Day 2: Tachycardia
Troponin I elevation	Yes	Yes
Troponin I elevation resolved?	Yes	Yes
ECHO assessment post-symptom onset	Normal	Normal
cMRI changes consistent with myocarditis?	Yes	cMRI not performed
Cardiac-related medication newly added to treatment regimen at hospital discharge	Yes	No
Post-episode LVEF% (ECHO)	Normal	Normal

cMRI, cardiac magnetic resonance imaging; DMD, Duchenne muscular dystrophy; ECHO, echocardiography; LVEF, left ventricular ejection fraction.

1. Potter RA, et al. *Sci Rep.* 2025;15(1):4.

Troponin I Levels

- Except in the 2 myocarditis cases, troponin I fluctuations in EMBARK were asymptomatic and compatible with fluctuations observed in DMD[1]



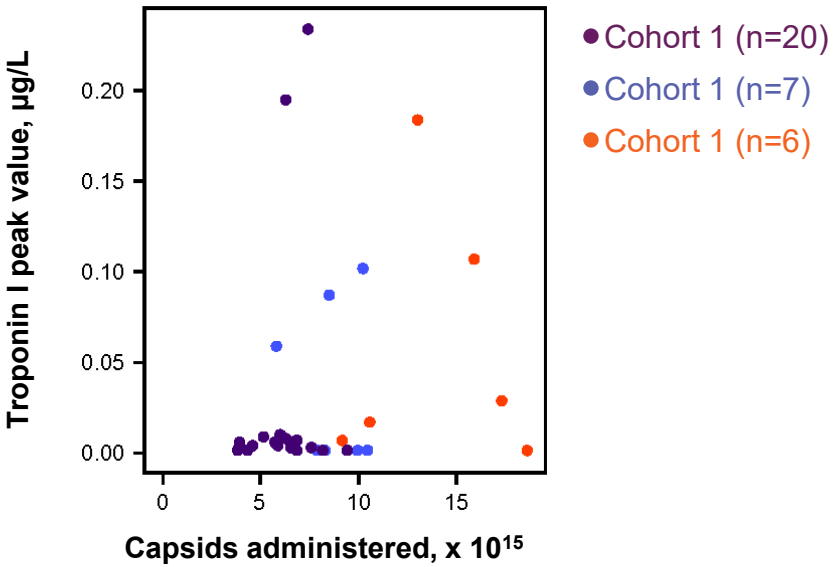
[a]Dotted lines indicate patients with more than 1 elevated troponin I value. For clarity, data from patients with troponin I values >1.3 µg/L are omitted from the enlarged image.
DMD, Duchenne muscular dystrophy.

1. Sheybani A, et al. *Pediatr Res.* 2022;92(6):1613-20.

Troponin I Levels

- An analysis of ENDEAVOR Cohorts 1-3 (n=33), which included 6 non-ambulatory patients, showed no apparent relationship between total capsid load and troponin levels at baseline, peak troponin I levels, or change in troponin I levels from baseline 1-2 weeks post-infusion
- There was also no apparent relationship between troponin I levels and serum vector genome exposure (as measured via C_{max})
- In ENDEAVOR and EMBARK Part 1, 12 out of 107 patients with available baseline and post-baseline ECHO data had elevated troponin I levels at baseline
  - One year post-infusion, only 1 of these patients had LVEF <50% (48% by ECHO)

Peak Troponin I in ENDEAVOR



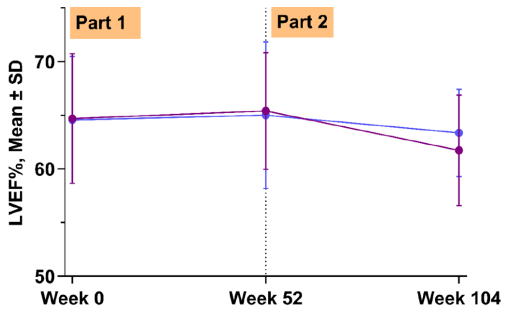
ECHO, echocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction.

Left Ventricular Function Assessed by cMRI

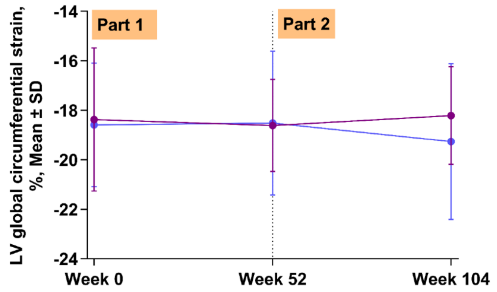
- LVEF were stable across all studies
- **EMBARK:** the cMRI substudy revealed no relevant differences in LV values between patients treated with delandistrogene moxeparvovec for up to 104 weeks and those treated with placebo for 52 weeks

EMBARK, cMRI Substudy (n=39)[a]

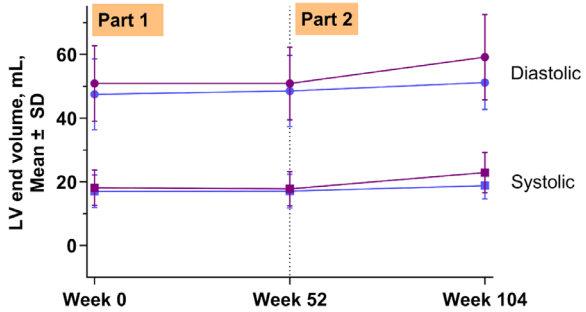
LVEF



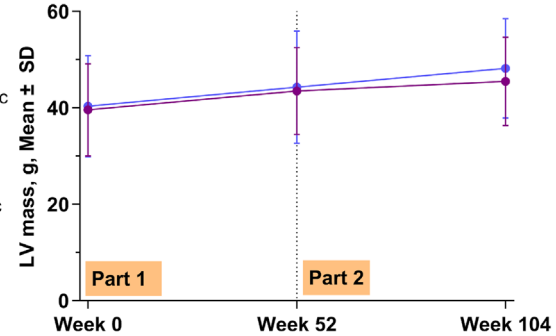
Global circumferential strain



EMBARK: LV ejection volume (cMRI)



EMBARK: LV mass (cMRI)



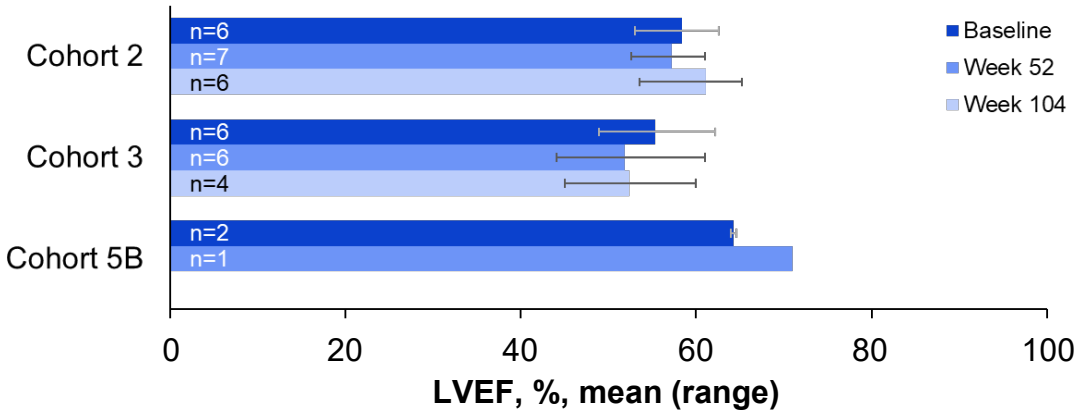
Delandistrogene moxeparvovec-treated patients in Part 1 (n=19)
Delandistrogene moxeparvovec-treated patients in Part 2 (n=20)

[a]Point estimates at the end of Part 1 (Week 52) were very similar but not identical to the point estimates for the baseline of Part 2. For clarity, only baseline Part 2 values are shown.
cMRI, cardiac magnetic resonance imaging; ECHO, echocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; SD, standard deviation.

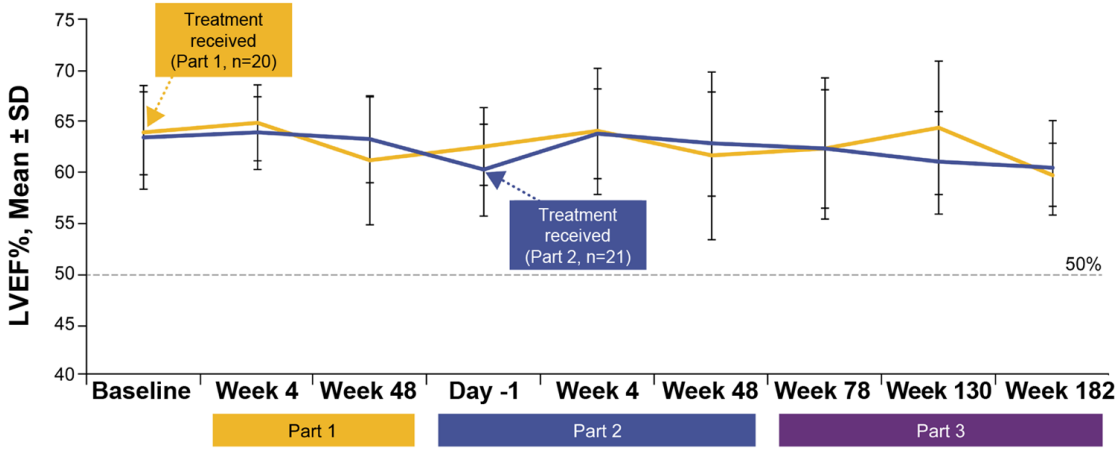
LVEF as Assessed by ECHO

- **ENDEAVOR:** ECHO revealed stable LVEF values over 2 years of follow-up
- **Study 102:** ECHO revealed stable LVEF values 3.5 years post-infusion
- **Study 101:** ECHO revealed that all 4 patients' LVEF remained normal (>50%) 5 years post-infusion

ENDEAVOR, Change in LVEF



Study 102, Change in LVEF (n=41)



cMRI, cardiac magnetic resonance imaging; ECHO, echocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; SD, standard deviation.

Conclusions and Overall Safety

Conclusions

- Results of clinical studies with up to 5 years of follow-up indicate a manageable cardiac safety profile of delandistrogene moxeparvovec in a predominantly ambulatory population of patients with DMD
- There have been no signs of persistent treatment-related cardiac injury with delandistrogene moxeparvovec

Overall safety

- Safety is manageable with appropriate monitoring and treatment of adverse events, which typically occur within 90 days of infusion
- 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

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DMD, Duchenne muscular dystrophy.