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

Aravindhan Veerapandiyan[1a]; John Bourke[2]; John Day[3]; Craig McDonald[4]; Jerry Mendell[5]; Jonathan Soslow[6]; Craig Zaidman[7]; Stefanie Mason[5]; Jianfeng Meng[5]; Mark Vivien[5]; Tao Niu[5]; Alexander P. Murphy[8]; Christoph Wandel[9]; James Richardson[5]

[1]University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR, USA; [2]NUTH NHS Hospitals Foundation Trust, Newcastle upon Tyne, UK; [3]Stanford University, Palo Alto, California, USA; [4]UC Davis, Davis, CA, USA; [5]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [6]Vanderbilt University Medical Center, Nashville, TN, USA; [7]Washington University in Saint Louis, Saint Louis, MO, USA; [8]Roche Products Ltd, Welwyn Garden City, UK; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland

[a]Presenting author

OBJECTIVE

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

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

METHODS

Patients

- Data were collected from 4 studies (**Table 1**):
  - 101 (NCT03375164; n=4)[7]
  - 102 (NCT03769116; n=41)[8]
  - ENDEAVOR (NCT04626674, Cohorts 1-5b; n=48)[9]
  - EMBARK, Parts 1 and 2 (NCT05096221; n=125)[10]
- All studies excluded patients with signs of cardiomyopathy, including an echocardiogram (ECHO) that indicated left ventricular ejection fraction (LVEF) <40%

Cardiac Assessments

Cardiac specific–monitoring included reporting of cardiac adverse events (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

RESULTS

Baseline Characteristics

- Data were collected from 218 patients, of whom 210 (96%) were ambulatory (**Table 1**)
- At baseline, participants' ages ranged from 3.2 to 20.2 years, and their LVEF values from 48.9% to 78.0% (**Table 1**)

Table 1. Baseline Characteristics of Patients With DMD Across Pooled Trials[a]

	Study 101 n=4	Study 102 n=41	Study 103 (ENDEAVOR) n=48						Study 301 (EMBARK) 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 duration, 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.

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 (**Table 2**)
- 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[4]

Table 2. Summary of 2 Patients Treated With Delandistrogene Moxeparvovec Who Experienced Myocarditis

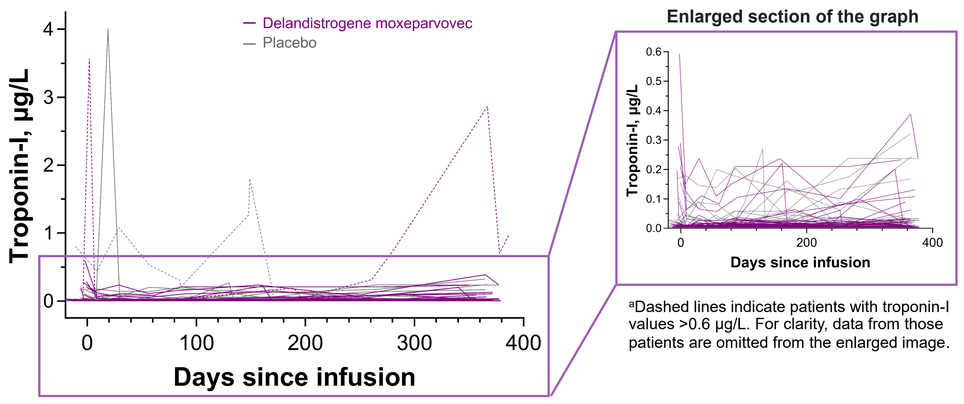
	Patient 1 (ENDEAVOR, Cohort 2)	Patient 2 (EMBARK, Part 1)
Age, years	11	6
Body mass, kg	50.5	20
Medical history	DMD-related cardiomyopathy (LVEF 60%)	Asthma, seasonal allergies
Post-treatment day of onset of myocarditis-related symptoms	Day 3: Nausea, vomiting Day 4: Troponin increase Day 6: Self-limited 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?	No	cMRI not performed
Medication added to treatment regimen post–hospital discharge?	No	Yes (propranolol)
Post-episode LVEF% (ECHO)	Normal	Normal

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

Troponin-I Levels

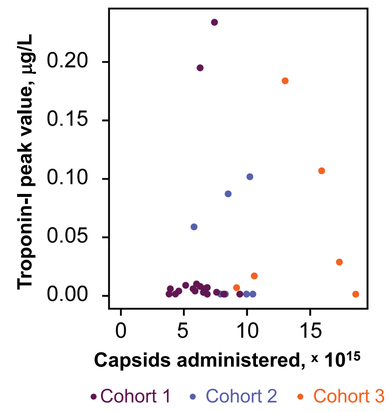
- Except in the 2 myocarditis cases, troponin-I fluctuations (EMBARK Part 1, **Figure 1**; ENDEAVOR, **Supplementary Figure S1**) were asymptomatic and compatible with fluctuations observed in DMD[11]
- An analysis of ENDEAVOR Cohorts 1-3 (n=33), which included 6 non-ambulatory patients, showed no apparent 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 (**Figure 2; Supplementary Figure S2**)
- 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)

Figure 1. Troponin-I Fluctuations in Patients From EMBARK Part 1[a]



[a]Dashed lines indicate patients with troponin-I values >0.6 µg/L. For clarity, data from those patients are omitted from the enlarged image.

Figure 2. Troponin-I Levels Versus Total Capsid Load in ENDEAVOR Cohorts 1-3

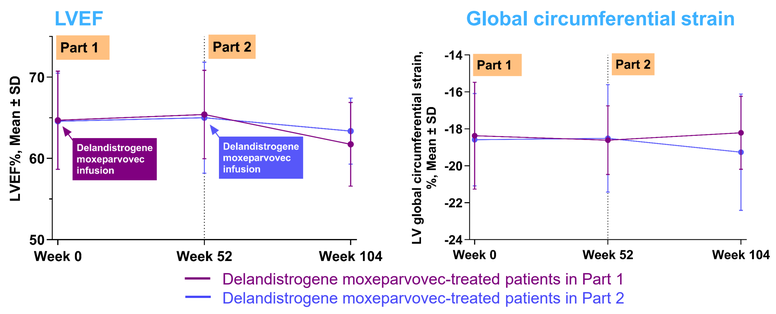


LVEF values were stable across all studies

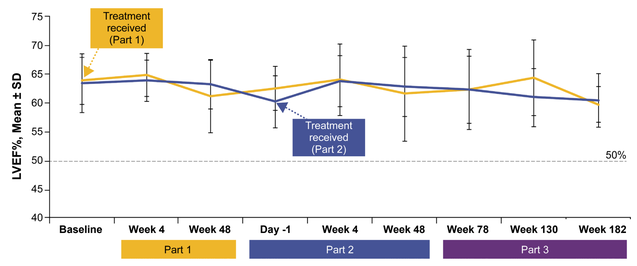
- **EMBARK:** the cMRI substudy revealed no relevant differences in LV values between patients treated with delandistrogene moxeparvovec for up to 104 weeks and those treated with placebo for 52 weeks (**Figure 3, Supplementary Figure S3**)
- **ENDEAVOR:** ECHO revealed stable LVEF values over 2 years of follow-up (**Supplementary Figure S3**)
- **Study 102:** ECHO revealed stable LVEF values 3.5 years post-infusion (**Figure 3**)
- **Study 101:** ECHO revealed that all 4 patients' LVEF remained normal (>50%) 5 years post-infusion

Figure 3. Changes in Left Ventricular Parameters Over Time: EMBARK and Study 102

EMBARK (cMRI): LVEF and global circumferential strain stable over 2 years of follow-up[a]



Study 102 LVEF (ECHO), stable over 3.5 years of follow-up



[a]In EMBARK cMRI substudy, the LV 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, echocardiography; LV, left ventricle; LVEF, left ventricular ejection fraction.

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**
- **Delandistrogene moxeparvovec treatment is generally well tolerated and safe, with no signs of persistent treatment-related cardiac injury**

Acknowledgments

- The authors would like to thank the patients and their families for their participation in these studies, as well as the investigators and trial staff involved
- Medical writing and editorial support were provided by Vojislav Pejović, PhD (Healthcare Consultancy Group) in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022), with funding from Sarepta Therapeutics, Inc., Cambridge, MA, USA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland
- Studies 101, 102, ENDEAVOR, and EMBARK are sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. ENDEAVOR and EMBARK are also funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland

Disclosures

A. Veerapandiyan has received honoraria for serving on advisory boards for Biogen and Novartis and receives research support from the Muscular Dystrophy Association and from Novartis; **J. Bourke** is a Data Monitoring Committee member for Sarepta gene-therapy trials and is a scientific advisor to Sarepta, Pfizer, Roche, and EspeRare Foundation; **C. McDonald** reports grants from Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics and has a consultancy/advisory role with BioMarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, and Sarepta Therapeutics. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics; **J. Mendell** received study funding from Sarepta Therapeutics while at Nationwide Children's Hospital at the time of the studies and is currently an employee of Sarepta Therapeutics; he is also a co-inventor of AAVrh74.MHCK7.micro-dys technology; **J. Day** and **J. Soslow** have no potential conflicts of interest to declare; **C. Zaidman** has received research support from Biogen and Novartis and has served on an advisory board for Sarepta Therapeutics; **S. Mason, J. Meng, M. Vivien, T. Niu,** and **J. Richardson** are Sarepta employees and may hold company stock; **A. P. Murphy** and **C. Wandel** are Roche employees and may hold company stock.

References

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.
7. Mendell JR, et al. *Muscle Nerve* 2024; 69(1): 93-8.
8. Mendell JR, et al. *Front Cell Dev Biol* 2023; 11: 1167762.
9. Zaidman CM, et al. *Ann Neurol* 2023; 94(5): 955-68.
10. Mendell JR, et al. *Nat Med* 2025; 31(1): 332-41.
11. Sheybani A, et al. *Pediatr Res* 2022; 92(6): 1613-20.

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Presented at the MDA Clinical and Scientific Conference 2025; March 16-19, 2025; Dallas, TX, USA.

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

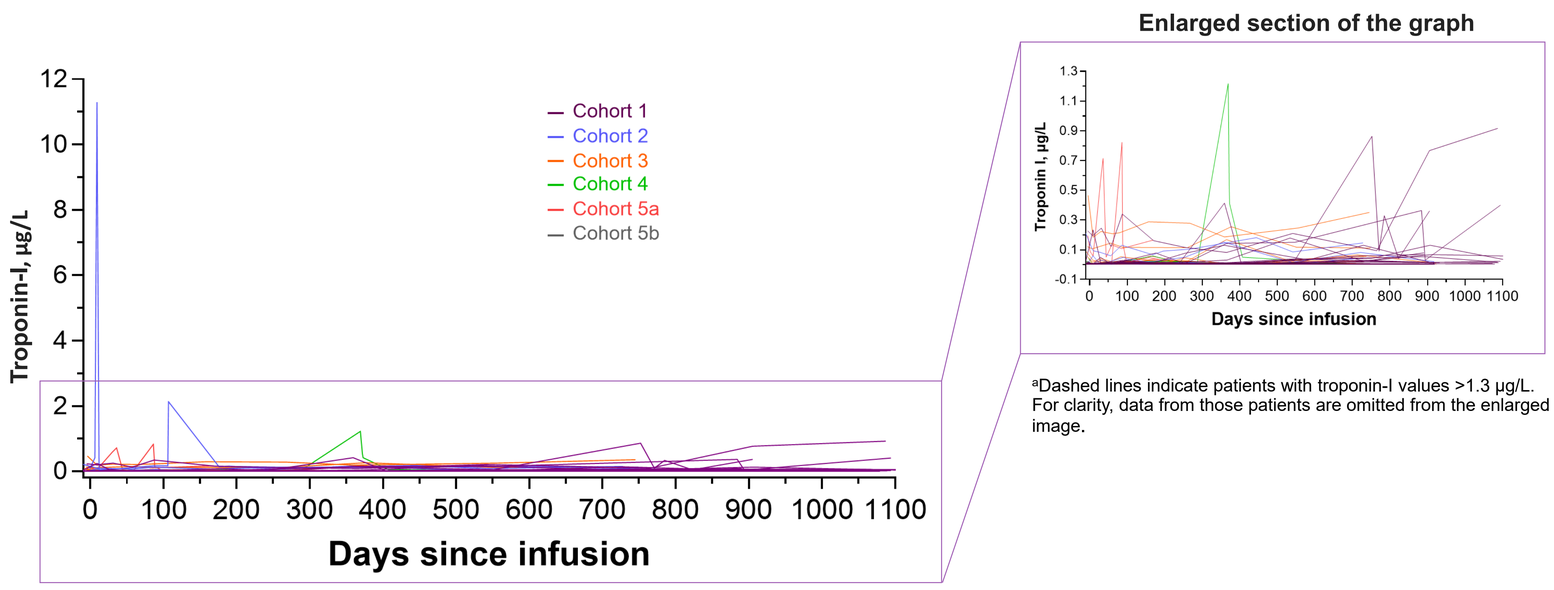
Aravindhan Veerapandiyan[1a]; John Bourke[2]; John Day[3]; Craig McDonald[4]; Jerry Mendell[5]; Jonathan Soslow[6]; Craig Zaidman[7]; Stefanie Mason[5]; Jianfeng Meng[5]; Mark Vivien[5]; Tao Niu[5]; Alexander P. Murphy[8]; Christoph Wandel[9]; James Richardson[5]

[1]University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR, USA; [2]NUTH NHS Hospitals Foundation Trust, Newcastle upon Tyne, UK; [3]Stanford University, Palo Alto, California, USA; [4]UC Davis, Davis, CA, USA; [5]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [6]Vanderbilt University Medical Center, Nashville, TN, USA; [7]Washington University in Saint Louis, Saint Louis, MO, USA; [8]Roche Products Ltd, Welwyn Garden City, UK; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland

[a]Presenting author

RESULTS

Figure S1. Troponin-I Fluctuations in Patients From ENDEAVOR[a]



[a]Dashed lines indicate patients with troponin-I values >1.3 µg/L. For clarity, data from those patients are omitted from the enlarged image.

Figure S2. Troponin-I Levels Versus Total Capsid Load in ENDEAVOR Cohorts 1-3

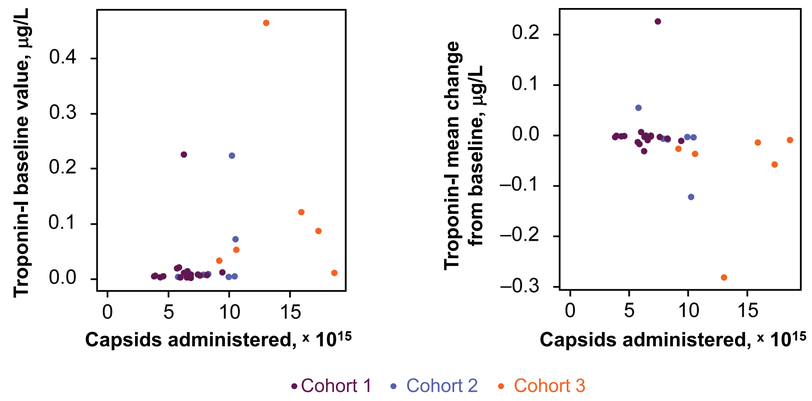
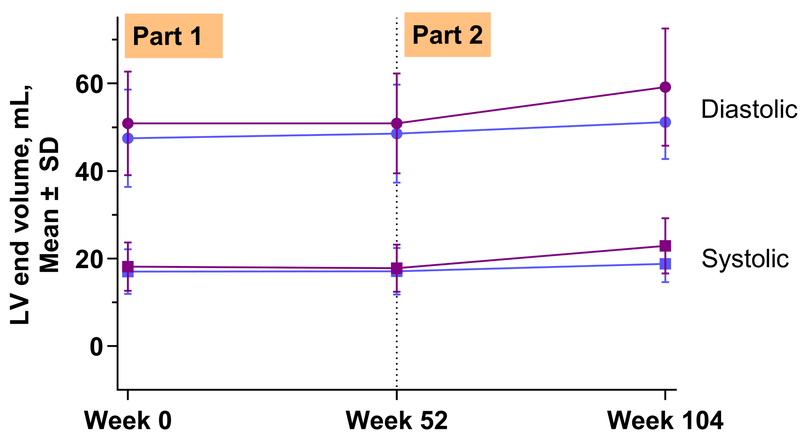
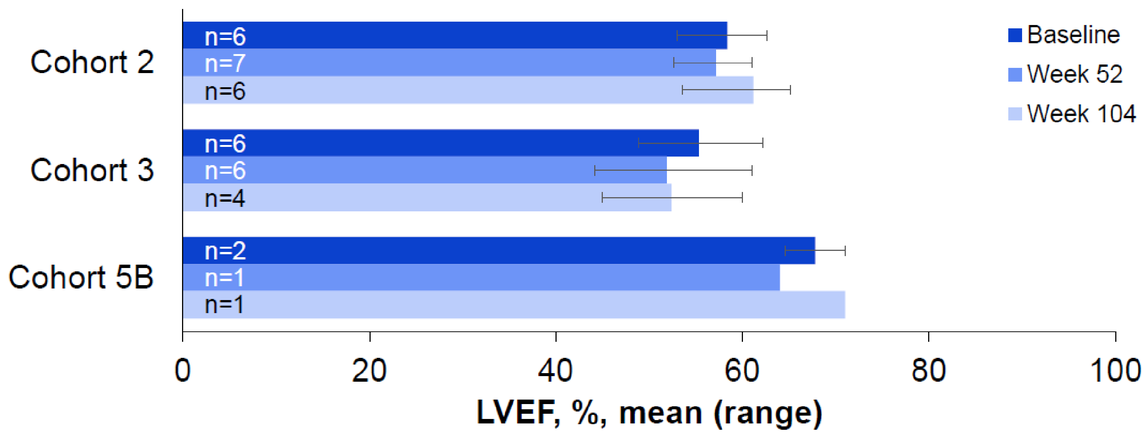


Figure S3. Change in Left Ventricular Parameters Over Time in EMBARK and ENDEAVOR

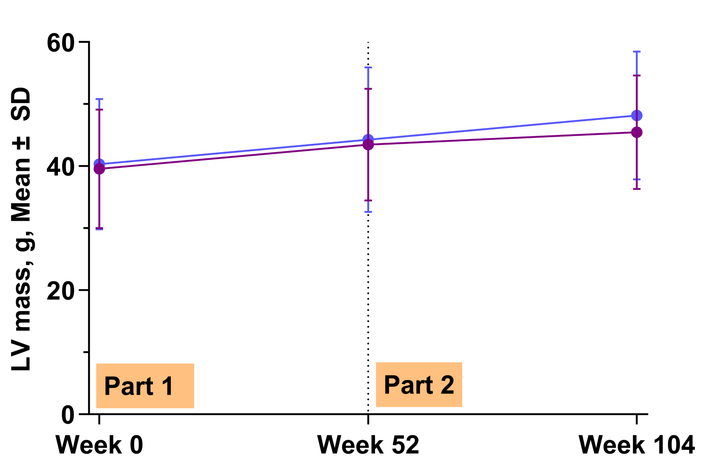
EMBARK: LV ejection volume (cMRI)



ENDEAVOR: LVEF (ECHO)



EMBARK: LV mass (cMRI)



Acknowledgments

- The authors would like to thank the patients and their families for their participation in these studies, as well as the investigators and trial staff involved
- Medical writing and editorial support were provided by Vojislav Pejović, PhD (Healthcare Consultancy Group) in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022), with funding from Sarepta Therapeutics, Inc., Cambridge, MA, USA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland
- Studies 101, 102, ENDEAVOR, and EMBARK are sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. ENDEAVOR and EMBARK are also funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland

Disclosures

A. Veerapandiyan has received honoraria for serving on advisory boards for Biogen and Novartis and receives research support from the Muscular Dystrophy Association and from Novartis; **J. Bourke** is a Data Monitoring Committee member for Sarepta gene-therapy trials and is a scientific advisor to Sarepta, Pfizer, Roche, and EspeRare Foundation; **C. McDonald** reports grants from Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics and has a consultancy/advisory role with BioMarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, and Sarepta Therapeutics. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics; **J. Mendell** received study funding from Sarepta Therapeutics while at Nationwide Children's Hospital at the time of the studies and is currently an employee of Sarepta Therapeutics; he is also a co-inventor of AAVrh74.MHCK7.micro-dys technology; **J. Day** and **J. Soslow** have no potential conflicts of interest to declare; **C. Zaidman** has received research support from Biogen and Novartis and has served on an advisory board for Sarepta Therapeutics; **S. Mason, J. Meng, M. Vivien, T. Niu,** and **J. Richardson** are Sarepta employees and may hold company stock; **A. P. Murphy** and **C. Wandel** are Roche employees and may hold company stock.

References

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.
7. Mendell JR, et al. *Muscle Nerve* 2024; 69(1): 93-8.
8. Mendell JR, et al. *Front Cell Dev Biol* 2023; 11: 1167762.
9. Zaidman CM, et al. *Ann Neurol* 2023; 94(5): 955-68.
10. Mendell JR, et al. *Nat Med* 2025; 31(1): 332-41.
11. Sheybani A, et al. *Pediatr Res* 2022; 92(6): 1613-20.

Presented at the MDA Clinical and Scientific Conference 2025; March 16-19, 2025; Dallas, TX, USA.