

Pooled Safety Analysis from Phase 1 to Phase 3 Clinical Trials of Delandistrogene Moxeparvovec in Duchenne Muscular Dystrophy

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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 slow disease progression in ambulatory patients with DMD1–4
- Delandistrogene moxeparvovec is approved for the treatment of ambulatory patients with DMD in the USA and in other select countries5,6
- Clinical trial experience has established a consistent profile for the frequency, types, and timing of potential safety events observed for this rAAVrh74 vector-based therapy (**Figure 1**)1,7,8
 - The innate immune response to delandistrogene moxeparvovec is activated within the first hours or days post-infusion, while the acquired immune response takes weeks to develop1,7,8
- Evidence to date suggests that the critical period for close monitoring for safety events is the first 90 days after infusion, and long-term safety continues to be monitored in these patients

Methods

- Safety and tolerability outcomes from patients treated with delandistrogene moxeparvovec with up to 7.5 years’ follow-up were collected from Study 101 (NCT03375164), Study 102 (NCT03769116), ENDEAVOR Cohorts 1–7 (NCT04626674), EMBARK (NCT05096221), and ENVOL Cohorts A and B (NCT06128564). Some patients had rolled over into the long-term follow-up EXPEDITION study (Study 305, NCT05967351)
- Data sources for the pooled safety analyses were the final database lock for all studies (excluding ENDEAVOR Cohorts 6 and 7) if patients were not followed in EXPEDITION. Data cutoffs were January 13, 2025 for ENDEAVOR Cohort 6 and February 1, 2025 for ENDEAVOR Cohort 7 if patients were not followed in EXPEDITION. Otherwise, the data cutoff for EXPEDITION (October 13, 2025) was used
- To be eligible, patients had to be on a stable dose of corticosteroids for ≥12 weeks prior to enrollment, except for patients in ENDEAVOR Cohorts 4 and 6 and ENVOL Cohorts A and B, which included only patients who had not reached the stage of chronic steroid use and who were not receiving steroids at the time of screening
- Patients could not be enrolled if they exhibited signs of cardiomyopathy (including an ECHO with an LVEF <40%) or if they had abnormal, clinically significant laboratory values

Results

- In total, 236 patients were included in the pooled analysis (ambulatory, n=227 [96.2%]; non-ambulatory, n=9 [3.8%]) (**Table 1**)
- The age range was 1.9–24.0 years, the weight range was 12.0–80.1 kg, and the LVEF range was 48.9–78.0%. The mean (range) follow-up duration across all studies was 3.2 (0.5–7.5) years
- Safety overview**
 - Most TR-TEAEs first appeared within the first 90 days post-infusion and resolved spontaneously or with appropriate intervention (**Table 2**)
 - Liver injury was the most frequently reported TR-SAE observed during the first 60 days post-infusion (**Figure 2; Supplementary Table 1**)
 - 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 age10
 - Troponin-I levels fluctuate, consistent with the natural history of DMD11 (**Supplementary Figure 1**)

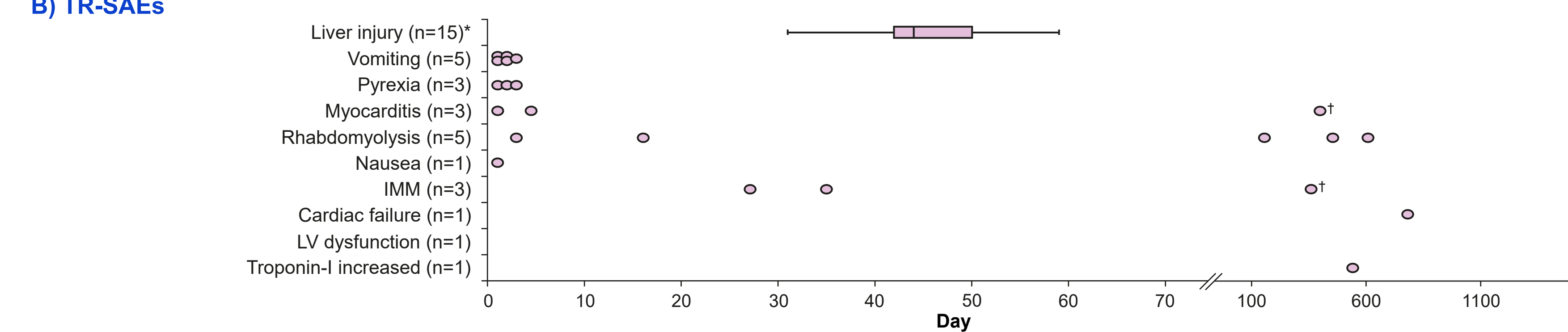
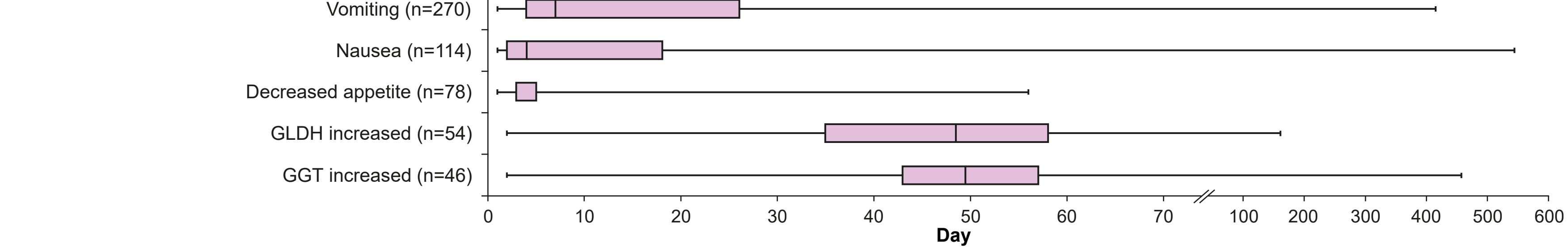
Table 1 Baseline demographics, clinical characteristics, and follow-up duration across clinical trials*														
	Study 101 (N=4)	Study 102 (N=41)	ENDEAVOR (Study 103)								EMBARC (Study 301)		ENVOL (Study 302)	
			Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)	Cohort 5a (N=6)	Cohort 5b (N=2)	Cohort 6 (N=6)	Cohort 7 (N=1)	Treated in Part 1 (N=63)	Treated in Part 2 (N=62) [†]	Cohort A (N=10)	Cohort B (N=3)
Inclusion criteria														
Age, years		≥4 to <8		≥8 to <18	No restriction	≥3 to <4	≥4 to <9	No restriction	≥2 to <3	No restriction	≥4 to <8	≥4 to <8	≥3 to <4	≥2 to <3
Ambulatory status		Ambulatory		Non-ambulatory		Ambulatory		Non-ambulatory	Ambulatory	Non-ambulatory		Ambulatory		Ambulatory
Genetic inclusion criteria, DMD gene		Frameshift (deletion or duplication) or premature stop codon mutation between exons 18 and 58		Pathogenic variant [‡] fully contained between exons 18 and 79 (inclusive) [§]			Pathogenic variant [‡] partially or fully contained between exons 1 and 17 (inclusive) [¶]		Pathogenic variant [‡] partially or fully contained between exons 1 and 17 (inclusive)		Pathogenic variant [‡] fully contained between exons 18 and 79 (inclusive) [†]		Pathogenic variant [‡] fully contained between exons 18 and 79 (inclusive)**	
Baseline demographics and clinical characteristics														
Age range, years	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	2.2–2.9	24.0	4.1–7.9	4.0–8.0	3.1–3.7	1.9–2.3
Weight range, kg	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	12.4–17.8	43.6	13.5–38.5	14.4–41.6	12.0–18.9	12.0–14.6
Mean (range) LVEF, %	60.7 ^{††} (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)		63.1 (61.0–68.0)	60.0	64.9 (55.0–77.0)	64.4 (52.0–78.0)	64.6 (56.0–75.0)	67.7 (67.0–69.0)
Mean (range) FVC, L	–	–	–	1.70 (1.23–2.29)	2.09 (1.57–3.09)	–	–	2.16 (1.89–2.42)	–	1.19	–	–	–	–
Mean (range) FVC, % predicted	–	–	–	97 (66–116)	78 (43–113)	–	–	85 (80–90)	–	28.3	–	–	–	–
Mean (range) PUL Version 2.0 total score	–	–	–	38.9 (33–42)	22.2 (18–31)	–	–	27.5 (21–34)	–	11	–	–	–	–
Mean (range) troponin-I, µg/L	–	–	0.02 ^{‡‡} (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)	0.01 (0.01–0.02)	0.04	0.03 ^{§§} (0–0.59)	0.03 (0–0.81)	0.02 (0.00–0.07)	0.02 (0.01–0.02)
Follow-up														
Mean (range) follow-up, years	5.0 (5.0–5.1)	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)	0.7 (0.7–0.7)	1.4 (1.4–1.4)	3.0 (2.1–3.8)	2.0 (0.7–2.6)	1.2 (1.0–1.7)	0.6 (0.5–0.7)
Data cutoff date	Jun 8, 2023	Sept 29, 2023	Jul 2, 2024	Aug 15, 2024			Jul 2, 2024		Jan 13, 2025		Feb 1, 2025	Oct 25, 2024		Aug 4, 2025
Study level baseline is used. *Data in this table do not comprehensively represent all ongoing trials. [†] For EMBARK Part 2, 62 patients received placebo in Part 1 but only 60 patients received delandistrogene moxeparvovec in Part 2. [‡] Expected to lead to absent dystrophin. [§] Initial inclusion criteria allowed for any mutations in DMD exons 1 through 79; however, an IMM event in a patient with a large deletion in the exons 1–17 region of the DMD gene prompted an update to the inclusion criteria. [¶] Excludes deletions that fully include exons 9–13. ^{**} Excludes mutations fully contained within exon 45. ^{††} Excludes in-frame deletions, in-frame duplications, and variants of uncertain significance. ^{‡‡} n=3. ^{§§} n=19. n=62. Data cutoff date: final database lock for Study 101 (Jun 8, 2023), Study 102 (Sept 29, 2023), ENDEAVOR Cohorts 1, 4, and 5 (Jul 2, 2024), ENDEAVOR Cohorts 2 and 3 (Aug 15, 2024), ENVOL (Aug 4, 2025) and EMBARK (Oct 25, 2024) if patients were not enrolled in EXPEDITION. Data cutoffs were Jan 13, 2025 for ENDEAVOR Cohort 6 and Feb 1, 2025 for ENDEAVOR Cohort 7 if patients were not followed in EXPEDITION. Otherwise, the data cutoff date for EXPEDITION (Oct 13, 2025) was used. Data extraction date: final database lock for Study 101 (Jun 8, 2023), Study 102 (Sept 29, 2023), ENDEAVOR Cohorts 1, 4, and 5 (Jul 2, 2024), ENDEAVOR Cohorts 2 and 3 (Oct 1, 2024) and EMBARK (Dec 13, 2024); and data cutoffs for ENDEAVOR Cohorts 6 (Jan 13, 2025) and 7 (Feb 1, 2025).														

Table 2 Number of patients with TR-TEAEs (≥15% of patients) and TR-SAEs, listed by frequency at 0–2 weeks, n (%)

	Ambulatory				Total non-ambulatory (N=9)	Total patients (N=236)	Ambulatory				Total non-ambulatory (N=9)	Total patients (N=236)	Ambulatory				Total non-ambulatory (N=9)	Total patients (N=236)	Ambulatory				Total non-ambulatory (N=9)	Total patients (N=236)								
	2~4 years (n=26)	4~8 years (n=169)	8~13 years (n=32)	Total ambulatory (N=227)			2~4 years (n=26)	4~8 years (n=169)	8~13 years (n=32)	Total ambulatory (N=227)			2~4 years (n=26)	4~8 years (n=169)	8~13 years (n=32)	Total ambulatory (N=227)			2~4 years (n=26)	4~8 years (n=169)	8~13 years (n=32)	Total ambulatory (N=227)										
Patients with any TR-TEAE	17 (65.4)	131 (77.5)	28 (87.5)	176 (77.5)	7 (77.8)	183 (77.5)	10 (38.5)	84 (49.7)	20 (62.5)	114 (50.2)	4 (44.4)	118 (50.0)	2 (7.7)	13 (7.7)	4 (12.5)	19 (8.4)	0	19 (8.1)	3 (11.5)	26 (15.4)	5 (15.6)	34 (15.0)	2 (22.2)	36 (15.3)	0	23 (13.6)	2 (6.3)	25 (11.0)	0	25 (10.6)		
TR-TEAEs (≥15% of patients), n (%)																																
Vomiting	11 (42.3)	90 (53.3)	23 (71.9)	124 (54.6)	6 (66.7)	130 (55.1)	4 (15.4)	40 (23.7)	7 (21.9)	51 (22.5)	2 (22.2)	53 (22.5)	0	6 (3.6)	1 (3.1)	7 (3.1)	0	7 (3.0)	0	6 (3.6)	0	6 (2.6)	0	6 (2.5)	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
Nausea	3 (11.5)	56 (33.1)	14 (43.8)	73 (32.2)	6 (66.7)	79 (33.5)	0	15 (8.9)	4 (12.5)	19 (8.4)	0	19 (8.1)	0	1 (0.6)	1 (3.1)	2 (0.9)	0	2 (0.8)	0	4 (2.4)	0	4 (1.8)	0	4 (1.7)	0	2 (1.2)	0	2 (0.9)	0	2 (0.8)		
Decreased appetite	7 (26.9)	46 (27.2)	8 (25.0)	61 (26.9)	1 (11.1)	62 (26.3)	2 (7.7)	9 (5.3)	4 (12.5)	15 (6.6)	0	15 (6.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
GLDH increased	0	7 (4.1)	3 (9.4)	10 (4.4)	0	10 (4.2)	1 (3.8)	24 (14.2)	5 (15.6)	30 (13.2)	1 (11.1)	31 (13.1)	0	4 (2.4)	0	4 (1.8)	0	4 (1.7)	2 (7.7)	4 (2.4)	0	6 (2.6)	2 (22.2)	8 (3.4)	0	0	0	0	0	0		
GGT increased (GGT >3×ULN)	0	0	1 (3.1)	1 (0.4)	0	1 (0.4)	2 (7.7)	22 (13.0)	7 (21.9)	31 (13.7)	1 (11.1)	32 (13.6)	0	4 (2.4)	1 (3.1)	5 (2.2)	0	5 (2.1)	0	0	1 (3.1)	1 (0.4)	0	1 (0.4)	0	2 (1.2)	0	2 (0.9)	0	2 (0.8)		
Patients with any TR-SAE	0	4 (2.4)	2 (6.3)	6 (2.6)	0	6 (2.5)	0	12 (7.1)	4 (12.5)	16 (7.0)	0	16 (6.8)	0	0	0	0	0	0	0	2 (1.2)	0	2 (0.9)	0	2 (0.8)	0	4 (2.4)	0	4 (1.8)	0	4 (1.7)		
TR-SAEs, n (%)																																
Liver injury*	0	0	0	0	0	0	0	10 (5.9)	3 (9.4)	13 (5.7)	0	13 (5.5)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Vomiting	0	3 (1.8)	2 (6.3)	5 (2.2)	0	5 (2.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Pyrexia	0	2 (1.2)	1 (3.1)	3 (1.3)	0	3 (1.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Mycocarditis	0	1 (0.6)	1 (3.1)	2 (0.9)	0	2 (0.8)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
Rhabdomyolysis	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
Nausea	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
IMM	0	0	0	0	0	0	0	1 (0.6)	1 (3.1)	2 (0.9)	0	2 (0.8)	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0		
Cardiac failure	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
LV dysfunction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
Troponin-I increased	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0	1 (0.4)	0	1 (0.4)		
Day 1 infusion	0~2 weeks						>2 weeks to 60 days						>60 days to 12 weeks						>12 weeks to Year 1						Year 1 to last follow-up							
*Reported terms for liver injury include GGT increased, hepatic enzyme increased, hepatotoxicity, hypertransaminasemia, liver injury, and transaminases increased.																																

Figure 2 Time to onset (median) of TR-TEAEs (≥15% of patients) and TR-SAEs in delandistrogene moxeparvovec clinical trials

A) TR-TEAEs (≥15% of patients)



*Reported terms for liver injury include GGT increased, hepatic enzyme increased, hepatotoxicity, hypertransaminasemia, liver injury, and transaminases increased.
†One patient exhibited a recurrence of IMM symptoms on Day 397 with additional cardiac involvement of myocarditis on Day 400 (troponin-I

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Supplementary information

Supplementary Table 1 Laboratory abnormalities of patients meeting criteria for acute liver injury

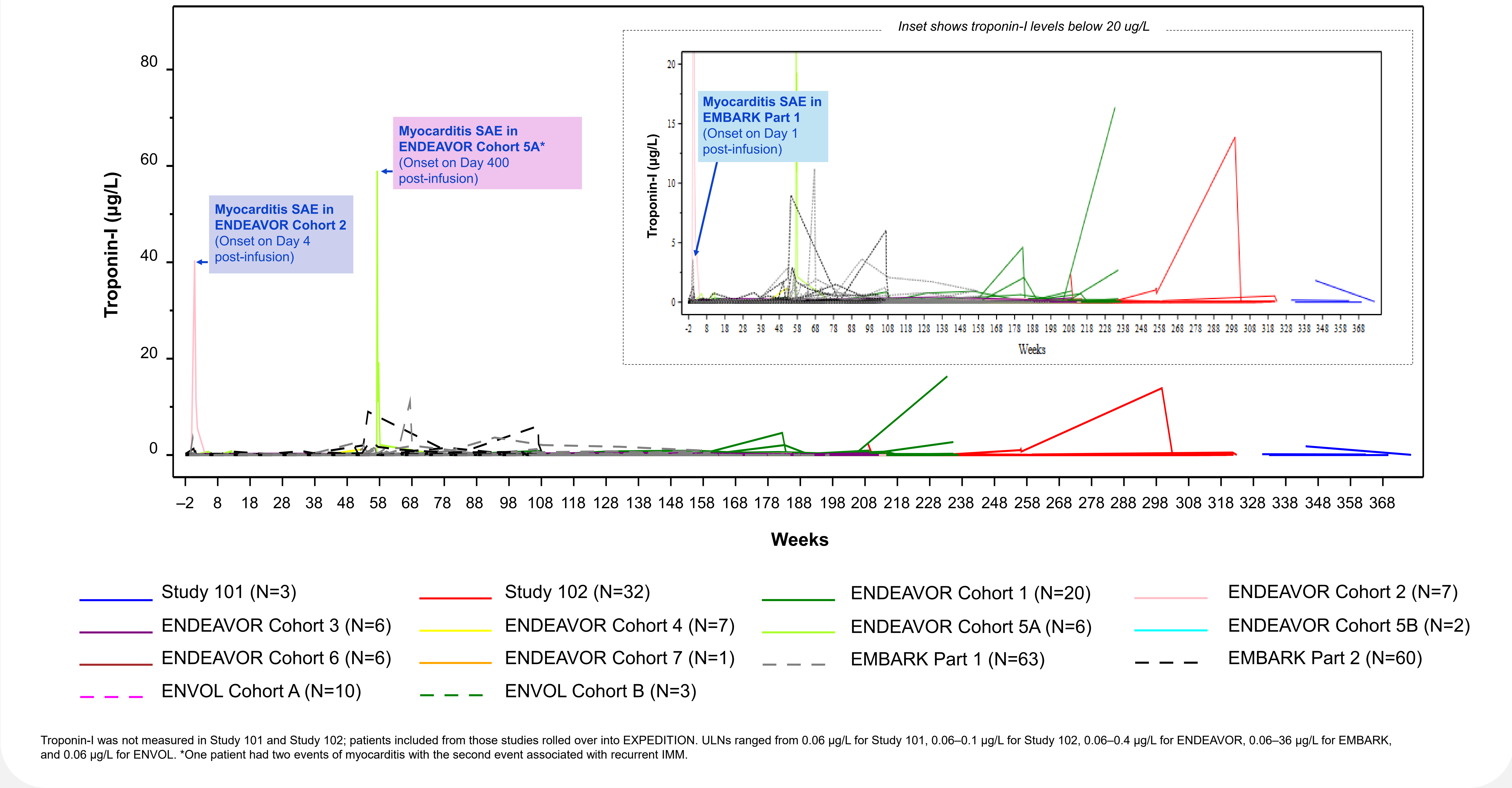
n (%)	Total patients (N=236)*
Patients meeting the definition of acute liver injury	110 (46.6)
GGT >3.0×ULN	38 (16.1)
GLDH >2.5×ULN*	100 (42.4)
ALT >3.0×BL†	27 (11.4)
ALP >2.0×ULN	1 (0.4)
Total bilirubin >2×ULN	7 (3.0)

*GLDH was not collected in Study 102 Part 1. †Excluding elevations from muscle.

Liver abnormalities of interest

- Liver function tests increased within 8 weeks after delandistrogene moxeparvovec infusion, with no clinically significant cases starting after 90 days
- Most hepatic laboratory parameters classified as AEs resolved either spontaneously or with corticosteroid treatment
- There were no instances of acute liver failure or confirmed elevations in the international normalized ratio in this pooled analysis
 - 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 [Study 303] trial and one in the commercial setting) at 15 and 16 years of age¹

Supplementary Figure 1 Troponin-I levels over time



Troponin-I levels

- Troponin-I levels were monitored regularly in the ENDEAVOR, EMBARK, ENVOL, and EXPEDITION studies only
- Troponin-I elevation was associated with definite, probable, or possible myocarditis SAEs that were deemed related to treatment that were observed in three patients (ENDEAVOR, n=2, 4 and 400 days post-infusion; EMBARK, n=1, 1-day post-infusion)
 - One patient experienced myocarditis following weaning of immunosuppression in the context of IMM, 400 days post-infusion²
- Fluctuations in troponin-I levels were consistent with the natural history of DMD³