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Long-term safety and tolerability of delandistrogene moxeparvovec in Duchenne muscular dystrophy: phase 1 to phase 3 clinical trials

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What does this study mean for the DMD community?

- This analysis adds to the body of evidence supporting the use of delandistrogene moxeparvovec for the treatment of early and late ambulatory as well as non-ambulatory patients with DMD, a patient population with a high unmet medical need

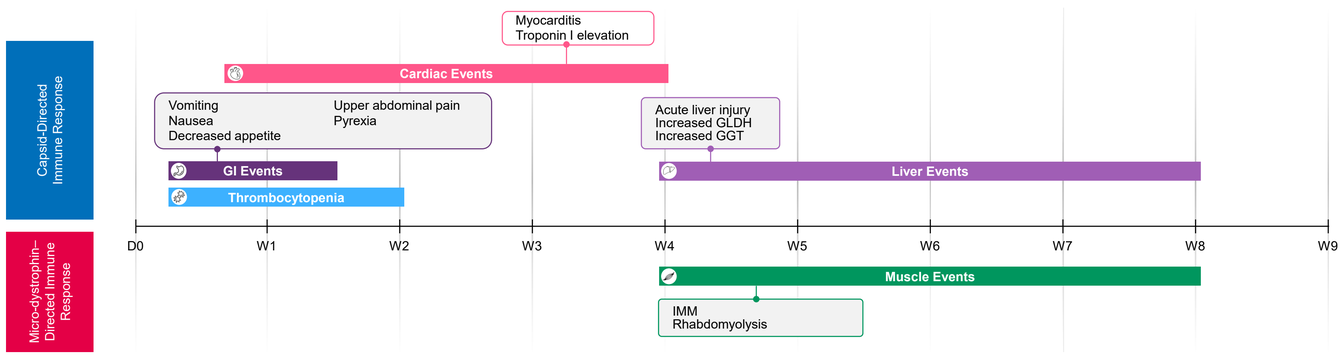
Conclusions

- Overall, delandistrogene moxeparvovec has a manageable and consistent safety and tolerability profile across a broad population of patients with DMD, regardless of age, weight, or disease stage
- Importantly, no deaths, study discontinuations, or clinically significant complement-mediated AEs have been observed in any studies of delandistrogene moxeparvovec, which utilizes the rAAVrh74 vector
- Based on this clinical trial experience, it is recommended to closely monitor patients for AEs within the first 90 days of delandistrogene moxeparvovec infusion
- The events of IMM, including the recurrence of IMM symptoms with additional cardiac involvement in one of the patients following weaning of immunosuppression, inform the current contraindication in patients with any deletion in exon 8 and/or exon 9 of *DMD*
- The long-term safety and tolerability profile of delandistrogene moxeparvovec will be continuously evaluated in EXPEDITION (NCT05967351), an ongoing phase 3 study which will follow approximately 400 patients from previous clinical trials for up to 5 years after delandistrogene moxeparvovec infusion[18]

BACKGROUND

- DMD is an X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in absent or insufficiently functional dystrophin[1]
- Delandistrogene moxeparvovec is an rAAVrh74 vector–based gene transfer therapy that delivers a transgene encoding micro-dystrophin, an engineered, functional form of dystrophin shown to stabilize or slow DMD progression[2-6]; it is approved in the US and in other select countries[7-13]
- Clinical trial experience in 156 patients has established a consistent profile for the frequency, types, and timing of potential safety events observed for this rAAVrh74 vector–based therapy (**Figure 1**)[6,14,15]
  - 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 develop[6,14,15]
- 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

Figure 1. Timeline of AEs Following Treatment With Delandistrogene Moxeparvovec and Their Association With Immune Responses[7,14,16]



OBJECTIVE

- To evaluate the long-term safety and tolerability of delandistrogene moxeparvovec in a broad DMD patient population based on clinical trial experience

METHODS

- Safety and tolerability outcomes from delandistrogene moxeparvovec–treated patients with DMD with up to 5 years' follow-up were collected from Studies 101 (NCT03375164) and 102 (NCT03769116), ENDEAVOR Cohorts 1-5 (NCT04626674), and EMBARK Part 1 (NCT05096221)
- Data sources for pooled analyses were Studies 101 and 102 (final data lock), ENDEAVOR (120-day safety update lock), and EMBARK Part 1 (120-day safety update lock), unless specified otherwise
- To be eligible, patients had to be on a stable dose of corticosteroids for ≥12 weeks prior to enrollment, except for the ENDEAVOR Cohort 4, which included only those 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 echocardiogram with a LVEF <40%) or if they had abnormal, clinically significant laboratory values

RESULTS

Baseline Data and Follow-up Duration

- In total, 156 patients were included in this pooled analysis (ambulatory, n=148 [95%]; non-ambulatory, n=8 [5%])
- The mean (range) age was 6.7 (3.2-20.2) years; the mean (range) weight was 24.6 (12.5-80.1) kg, and the LVEF range was 48.9%-77.0% (**Table 1; Supplement, Table S1**)
- The mean (range) follow-up duration across all studies was 2.4 (0.7-5.0) years

Table 1. Baseline Demographics, Clinical Characteristics, and Follow-up Duration Across Clinical Trials[a]

	Study 101 n=4	Study 102 n=41	Study 103 (ENDEAVOR) n=48						Study 301 (EMBARK) Part 1 n=63
			Cohort 1 n=20	Cohort 2 n=7	Cohort 3 n=6	Cohort 4 n=7	Cohort 5a n=6	Cohort 5b n=2	
Age eligibility	≥4 to <8 years	≥4 to <8 years	≥4 to <8 years	≥8 to <18 years	No restriction	≥3 to <4 years	≥4 to <9 years	No restriction	≥4 to <8 years
Ambulatory	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Genetic inclusion, *DMD* gene	Frameshift (deletion or duplication) or premature stop codon mutation between exons 18 and 58		Pathogenic variant[b] fully contained between exons 18 and 79 (inclusive)[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 (inclusive)[e]
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	4.1-7.9
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	13.5-38.5
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)
FVC mean (range), L	–	–	–	1.70 (1.23-2.29)	2.09 (1.57-3.09)	–	–	2.16 (1.89-2.42)	–
FVC mean (range), % predicted	–	–	–	97 (66-116)	78 (43-113)	–	–	85 (80-90)	–
PUL 2.0 total score, mean (range)	–	–	–	38.9 (33-42)	22.2 (18-31)	–	–	27.5 (21-34)	–
Troponin I mean (range), µg/L	–	–	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)
Follow-up mean (range), years	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)

[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 IMM 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.

Safety Overview

- The safety profile of delandistrogene moxeparvovec is consistent across patients regardless of age or ambulatory status (**Table 2**)
  - Among the TR-TEAEs that occurred in >15% of patients, GI events occurred most frequently and impacted the greatest number of patients
  - Liver abnormalities (hepatobiliary disorders and increased liver investigations) were the most frequently reported TR-SAEs by both patient and event count

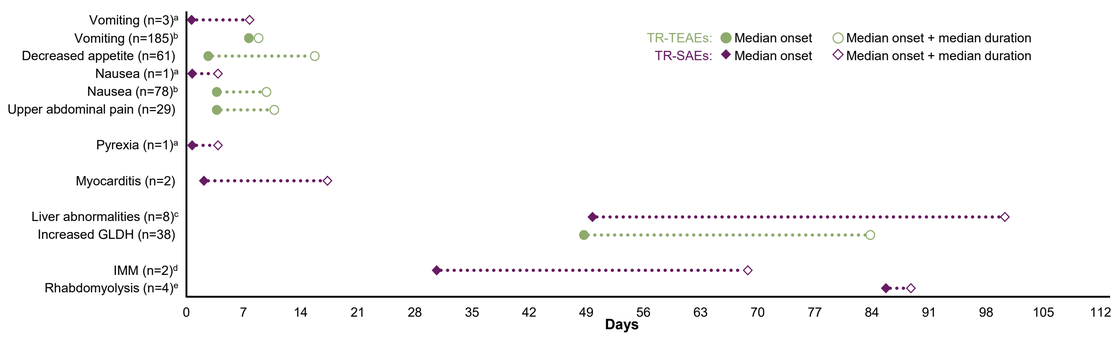
Table 2. AE Overview by Age and Ambulatory Status at Baseline

	Ambulatory, 3–7 years old[a] (n=141)	Ambulatory, 8–13 years old[b] (n=7)	Non-ambulatory, 9–21 years old[c] (n=8)	Total (N=156)	
	Patients, n (%)	Patients, n (%)	Patients, n (%)	Patients, n (%)	Events, n
TR-TEAEs (occurrence >15%)	**109 (77)**	**5 (71)**	**7 (88)**	**121 (78)**	**391**
GI	97 (69)	5 (71)	6 (75)	108 (69)	292
Vomiting	84 (60)	3 (43)	5 (62)	92 (59)	185
Nausea	51 (36)	4 (57)	5 (62)	60 (38)	78
Upper abdominal pain	22 (16)	1 (14)	1 (12)	24 (15)	29
Metabolism and nutrition	52 (37)	0	1 (12)	53 (34)	61
Decreased appetite	52 (37)	0	1 (12)	53 (34)	61
Investigations	30 (21)	1 (14)	3 (38)	34 (22)	38
Increased GLDH	30 (21)	1 (14)	3 (38)	34 (22)	38
TR-SAEs[d]	**13 (9)**	**2 (29)**	**0**	**15 (10)**	**21**
GI	2 (1)	1 (14)	0	3 (2)	4
Vomiting	2 (1)	1 (14)	0	3 (2)	3
Nausea	1 (0.7)	0	0	1 (0.6)	1
General disorders	1 (0.7)	0	0	1 (0.6)	1
Pyrexia	1 (0.7)	0	0	1 (0.6)	1
Hepatobiliary	5 (4)	0	0	5 (3)	5
Hypertransaminasemia	2 (1)	0	0	2 (1)	2
Liver injury	2 (1)	0	0	2 (1)	2
Hepatoxicity	1 (0.7)	0	0	1 (0.6)	1
Investigations	3 (2)	0	0	3 (2)	3
Increased GGT	1 (0.7)	0	0	1 (0.6)	1
Increased hepatic enzyme	1 (0.7)	0	0	1 (0.6)	1
Increased transaminases	1 (0.7)	0	0	1 (0.6)	1
Cardiac	1 (0.7)	1 (14)	0	2 (1)	2
Myocarditis	1 (0.7)	1 (14)	0	2 (1)	2
Musculoskeletal	4 (3)	1 (14)	0	5 (3)	6
Rhabdomyolysis	3 (2)	0	0	3 (2)	4
IMM	1 (0.7)[e]	1 (14)[f]	0	2 (1)	2

[a]Includes patients from Studies 101 and 102, ENDEAVOR (Cohorts 1, 4, 5a), and EMBARK Part 1. One patient from ENDEAVOR Cohort 5a was 8.6 years old at baseline. [b]Includes patients from ENDEAVOR (Cohorts 2, 5a). [c]Includes patients from ENDEAVOR (Cohorts 3, 5b). [d]TR-SAEs are a subset of all TR-TEAEs. [e]One patient from ENDEAVOR Cohort 5a exhibited a recurrence of IMM symptoms on D397 with additional cardiac involvement on D400 (troponin I elevation, chest pain) following weaning of immunosuppression 13 months post dosing. Symptoms stabilized approximately 2 weeks later, following modification of immunosuppression, while the patient remained hemodynamically stable. Cardiac MRI post discharge showed new LGE with normal LVEF. Because this recurrence of symptoms occurred after the dataset cutoff date (January 15, 2024), it is not reflected in the table. [f]The patient from ENDEAVOR Cohort 2 who experienced IMM was weaned off immunosuppression around D980 without re-emergence of IMM symptoms.

- Most TR-TEAEs occurred within 90 days of delandistrogene moxeparvovec infusion and resolved spontaneously or with appropriate management (**Figure 2**)

Figure 2. Timeline of Pooled Safety: TR-TEAEs and TR-SAEs



The figure represents the timelines of TR-TEAEs that occurred in >15% of delandistrogene moxeparvovec–treated patients and all TR-SAEs. The numbers in parentheses reflect the numbers of events. [a]One patient experienced TR-SAEs of nausea, vomiting, and pyrexia, which prompted hospitalization on D1. [b]At the time of the data cutoff, one patient had an unresolved vomiting event, which was not included in the median duration data point. [c]Includes hypertransaminasemia, liver injury, hepatotoxicity, increased GGT, increased hepatic enzyme, and increased transaminases. [d]One patient from ENDEAVOR Cohort 5a exhibited a recurrence of IMM symptoms on D397 with additional cardiac involvement on D400 (troponin I elevation, chest pain) following weaning of immunosuppression 13 months post dosing. Symptoms stabilized approximately 2 weeks later, following modification of immunosuppression, while the patient remained hemodynamically stable. Cardiac MRI post discharge showed new LGE with normal LVEF. Because this recurrence of symptoms occurred after the dataset cutoff date (January 15, 2024), it is not reflected in the figure. The other patient who experienced IMM, from ENDEAVOR Cohort 2, was weaned off immunosuppression around D980 without re-emergence of IMM symptoms. [e]Onset range for rhabdomyolysis was 3-457 days.

Liver Abnormalities of Interest

- Liver enzyme elevations (**Table 3**) were observed within 8 weeks after delandistrogene moxeparvovec infusion, with no clinically significant cases after 90 days
  - All 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

Table 3. Laboratory Abnormalities Indicative of Acute Liver Injury

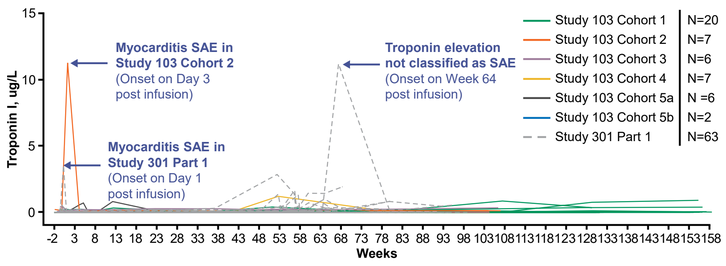
	All Patients N=156
Acute liver injury, n (%)	**65 (42)**
GGT >3×ULN	25 (16)
GLDH >2.5×ULN[a]	55 (35)
ALP >2×ULN	1 (0.6)
ALT >3×BL[b]	22 (14)
Total bilirubin >2×ULN, n (%)	**4 (3)**

[a]GLDH was not collected in Study 102 Part 1. [b]Excluding elevations from muscle.

Troponin I Levels

- Troponin I levels were monitored regularly in the ENDEAVOR and EMBARK studies only
- Early acute troponin I elevation was observed in 2 patients (ENDEAVOR, n=1, 3 days post infusion; EMBARK, n=1, 1 day post infusion), consistent with the recorded myocarditis TR-SAEs (**Figure 3**)
- Mild fluctuations in troponin I levels (**Figure 3**) are consistent with the natural history of DMD[17]

Figure 3. Troponin I Levels Over Time



Troponin I was not measured in studies 101 and 102. ULN was defined as 0.06 ug/L for Studies 103 and 301.

LVEF

- LVEF values were generally stable across studies (**Supplement, Figure S1**; Studies 102 and ENDEAVOR Cohort 3)
  - LVEF data from patients in ENDEAVOR Cohorts 2 and 5b and EMBARK Part 1 can be viewed in posters 424P and 428P, respectively (presentations: Wednesday, October 9 from 17:15 to 18:15)

Complement Activation

- No deaths, study discontinuations, or clinically significant AEs related to complement activation have been observed in any clinical studies of delandistrogene moxeparvovec
- On average, complement levels declined during the first week after delandistrogene moxeparvovec infusion, but returned to BL levels by week 2 (**Supplement, Figure S2**; ENDEAVOR data only)

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CP participated in advisory boards and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; and is a principal investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock. **CMM** 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. **EMM** has received fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. **FM** has received honoraria and grants from Sarepta Therapeutics for participating in symposia and advisory boards and is involved as an investigator in Sarepta Therapeutics clinical trials. He reports participation in advisory boards for Novartis, F. Hoffmann-La Roche Ltd, Edgewise Therapeutics, Dyne Therapeutics, Pfizer, PTC Therapeutics, and Italfarmaco. **CMZ** has received research support from Biogen and Novartis and has served on an advisory board for Sarepta Therapeutics. **SD**, **SM**, **JM**, and **EP** are employees of Sarepta Therapeutics and may have stock options. **APM** and **CR** are employees of Roche Products Ltd and may have stock options in F. Hoffmann-La Roche Ltd. **CW** is an employee of F. Hoffmann-La Roche Ltd and may have their stock options. **JRM** 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. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abbreviations

AE, adverse event; **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **D**, day; **DMD**, Duchenne muscular dystrophy; ***DMD***, dystrophin gene; **FVC**, forced vital capacity; **GGT**, gamma-glutamyl transferase; **GI**, gastrointestinal; **GLDH**, glutamate dehydrogenase; **IMM**, immune-mediated myositis; **LGE**, late gadolinium enhancement; **LVEF**, left ventricular ejection fraction; **MRI**, magnetic resonance imaging; **PUL 2.0**, performance of upper limb module for Duchenne muscular dystrophy 2.0; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **TR**, treatment-related; **ULN**, upper limit of normal; **W**, week.

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Presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia and virtual.

726LBP

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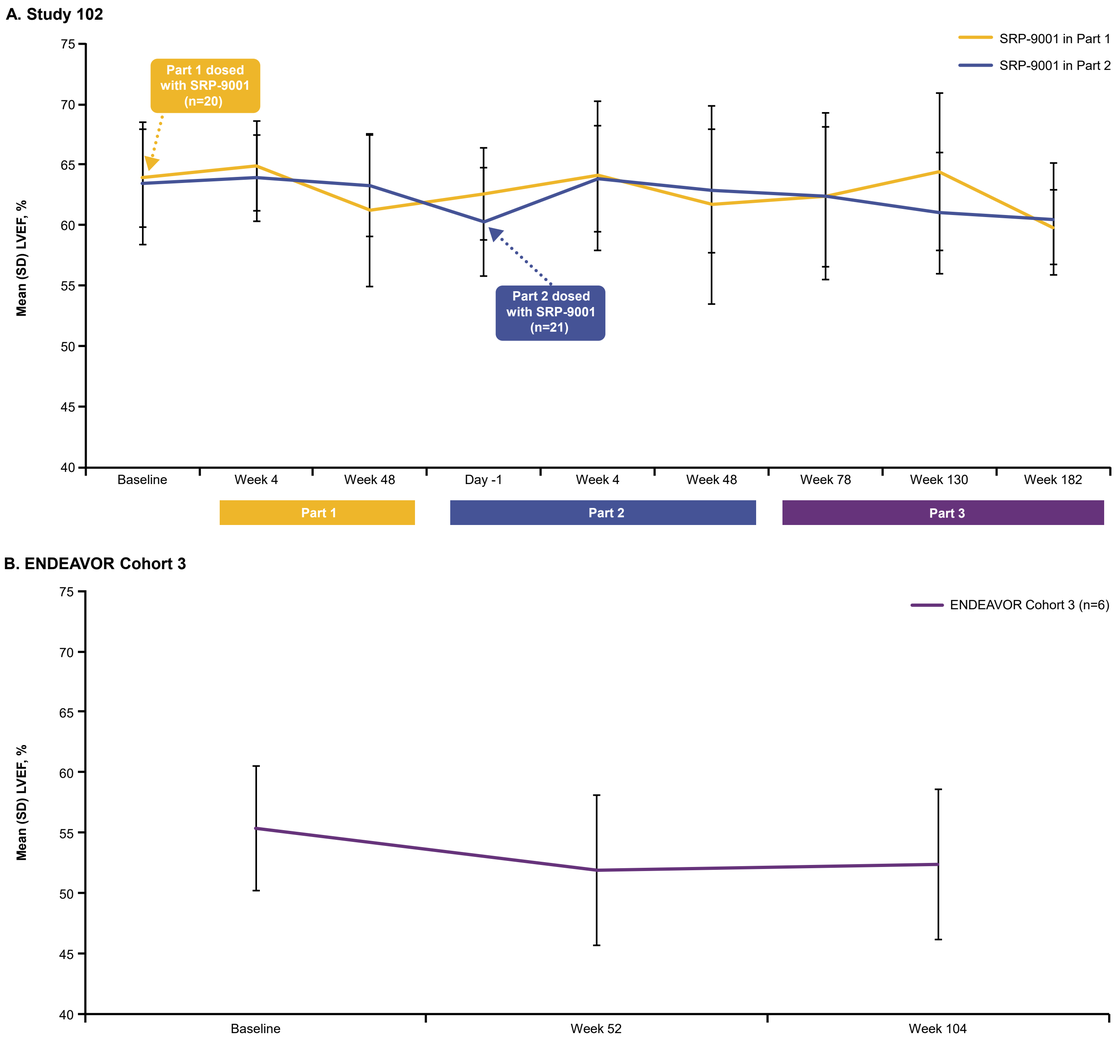
SUPPLEMENTARY INFORMATION

Table S1. Baseline Liver Function Test Values Across Clinical Trials[a]

	Study 101 n=4	Study 102 n=41	Study 103 (ENDEAVOR) n=48						Study 301 (EMBARK) Part 1 n=63
			Cohort 1 n=20	Cohort 2 n=7	Cohort 3 n=6	Cohort 4 n=7	Cohort 5a n=6	Cohort 5b n=2	
GGT mean (range), U/L	5.0 (5-5)	10.8[b] (5-17)	8.7 (5-21)	10.1 (7-20)	17.8 (7-41)	6.7 (6-8)	9.8 (7-14)	13.0 (10-16)	8.1 (4-17)
ALP mean (range), U/L	106 (85-120)	85[b] (41-132)	121 (70-192)	88 (38-226)	100 (64-135)	176 (119-225)	114 (85-159)	70 (41-100)	100 (53-295)
ALT mean (range), U/L	558 (387-801)	525[b] (47-1242)	580 (251-999)	310 (177-532)	93 (42-147)	442 (220-733)	544 (336-878)	124 (107-141)	498[c] (251-986)
Total bilirubin mean (range), mg/dL	0.30 (0.2-0.4)	0.32[b] (0.1-0.9)	0.26 (0.1-1)	0.40 (0.2-0.9)	0.18 (0.1-0.3)	0.21 (0.1-0.5)	0.20 (0.1-0.4)	0.15 (0.1-0.2)	0.26 (0.09-1.14)

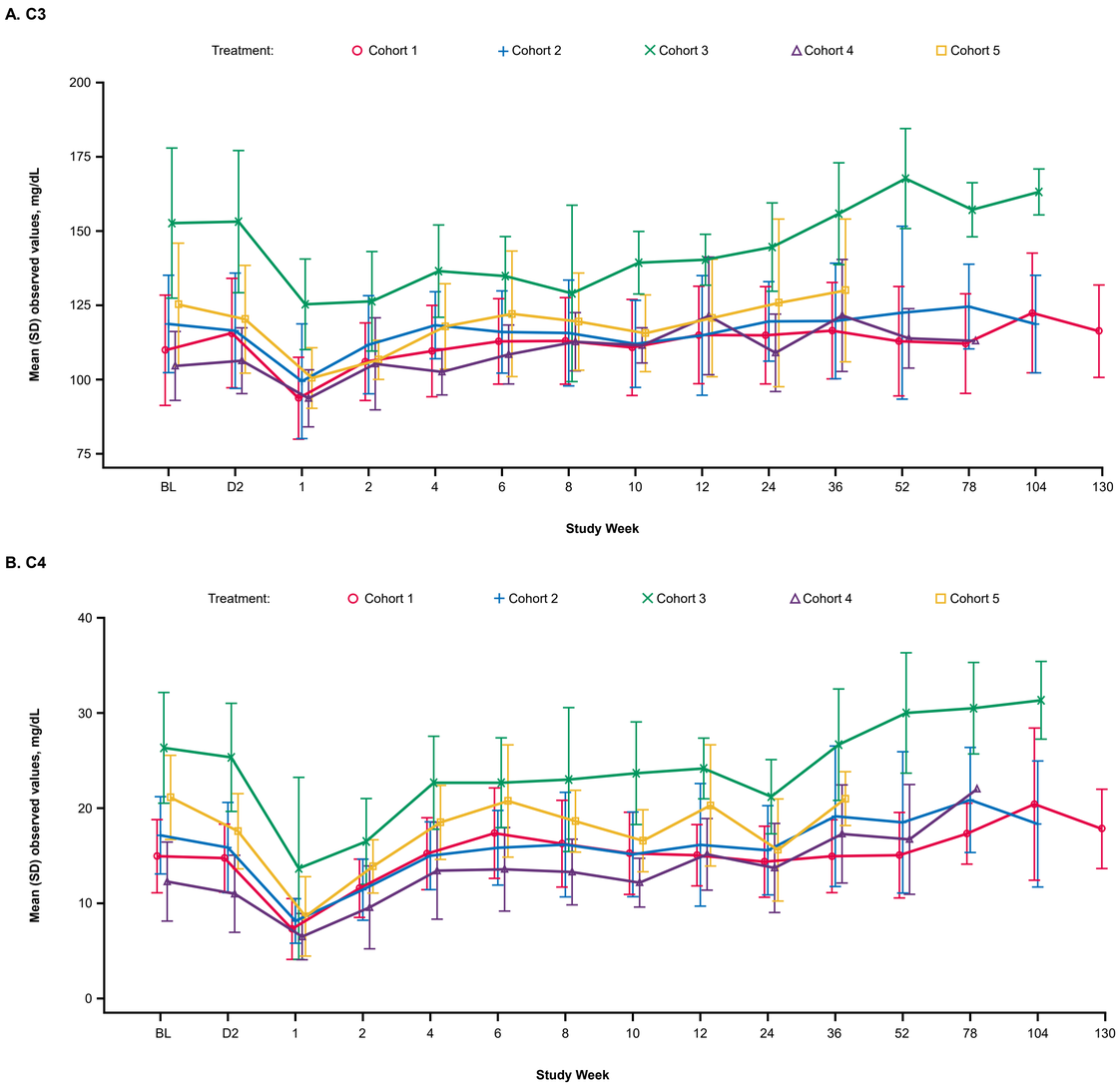
[a]Data in this table do not comprehensively represent all ongoing trials. [b]n=20. [c]n=62.

Figure S1. LVEF Values Over Time



LVEF was measured using an echocardiogram. Normal LVEF ranges from 50% to 70%.

Figure S2. Complement Levels in Patients From ENDEAVOR Cohorts 1-5b



Abbreviations

ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **BL**, baseline; **C**, complement; **D**, day; **GGT**, gamma-glutamyl transferase; **LVEF**, left ventricular ejection fraction.

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