Muscle MRI Outcomes in Patients with Duchenne Muscular Dystrophy Treated with Delandistrogene Moxeparvovec: Findings from EMBARK Part 1

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- Data were previously presented at the 29th Annual Congress of the World Muscle Society (WMS), October 8−12, 2024, Prague, Czechia

Background

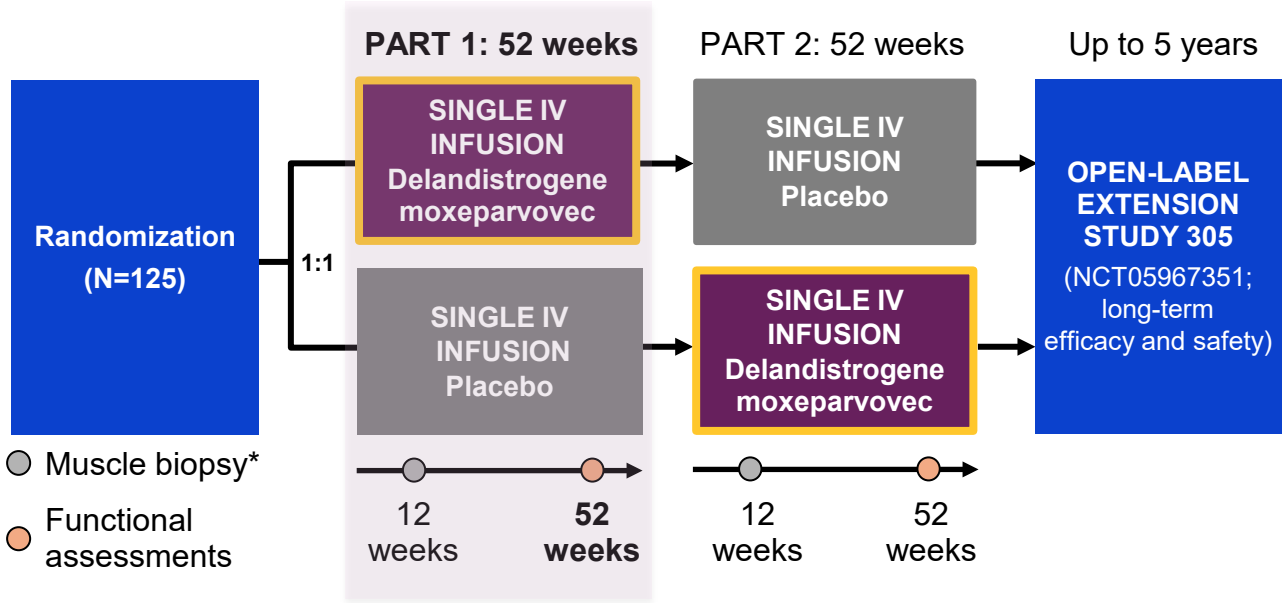
- DMD is a rare, X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in the absence of functional dystrophin[1]
  - Muscles are susceptible to repeated necrosis and regeneration cycles, which diminish the regenerative capacity of muscle cells, ultimately leading to fibrosis, the replacement of muscle with fat and connective tissue[2,3]
- 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 stabilize or slow disease progression in DMD[4–7]
  - It is approved in the USA and in other select countries[8–14]
- **EMBARK is a Phase 3, randomized, placebo-controlled trial** of delandistrogene moxeparvovec in ambulatory patients with DMD aged ≥4 to <8 years[7,15]

- We present pre-specified, exploratory analyses of muscle health and changes in **muscle pathology assessed by MRI in EMBARK Part 1** to further evaluate the effect of delandistrogene moxeparvovec treatment on DMD disease progression

DMD, Duchenne muscular dystrophy; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus serotype 74.

1. Duan D, et al. *Nat Rev Dis Primers*. 2021; 7:13; 2. Pessina P, et al. *Skelet Muscle*. 2014; 4:7; 3. Rooney WD, et al. *Neurology*. 2020; 94:e1622–e1633; 4. Asher DR, et al. *Expert Opin Biol Ther*. 2020; 20:263–274; 5. Zheng C and Baum BJ. *rehods Mol Biol*. 2008; 434:205–219; 6. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131; 7. Mendell JR, et al. *Nat Med*. 2025; 31:332–341; 8. US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information (Accessed March 2025); 9–14. Qatar Ministry of Public Health Update, UAE Ministry of Health & Prevention, Kuwait Ministry of Health Update, National Health Regulatory Authority Bahrain, Ministry of Health Oman, Ministry of Health Israel. Roche data on file; 15. ClinicalTrials.gov. NCT05096221 (Accessed March 2025).

EMBARK study design



Stratification was based on age at randomization (≥4 to <6 or ≥6 to <8 years) and NSAA total score at screening (≤22 or >22)

Key inclusion criteria

- Ambulatory males aged ≥4 to <8 years at randomization
- Confirmed DMD diagnosis (*DMD* mutation fully contained within exons 18–79 [inclusive])
- Able to cooperate with motor assessment testing
- NSAA total score >16 and <29 points at screening
- TTR <5 seconds at screening
- On a stable daily dose of oral corticosteroids for ≥12 weeks before screening
- rAAVrh74 total binding antibody titers <1:400

Exploratory MR endpoints

Change in quantitative muscle MRI findings from baseline to Week 52 (Part 1)

- Subset of 39 EMBARK participants
- Sites pre-selected based on quantitative MRI experience
- Not powered for statistical testing of MR parameters

*Only a subset of patients received a muscle biopsy for expression assessments, based on site experience and feasibility.
DMD, Duchenne muscular dystrophy; IV, intravenous; MR, magnetic resonance; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus serotype 74; TTR, Time to Rise.

1. Walter G, et al. Presented at WMS 2024; Poster 428P.

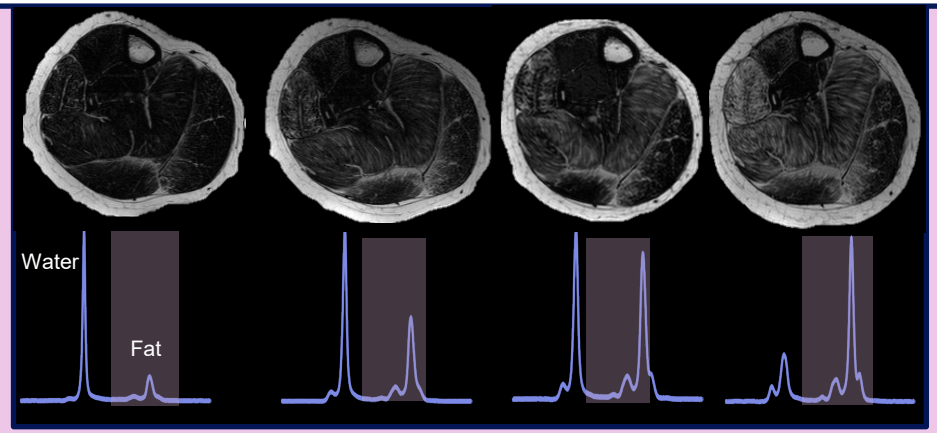
MR exploratory endpoints

MR is a non-invasive method to monitor DMD disease progression

- Sensitive to subclinical disease progression
- Not dependent on patient growth, maturation, or motivation

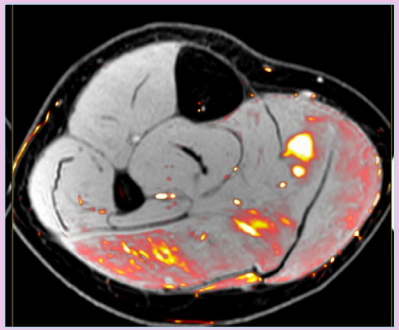
EMBARK MR endpoints included biomarkers of muscle health

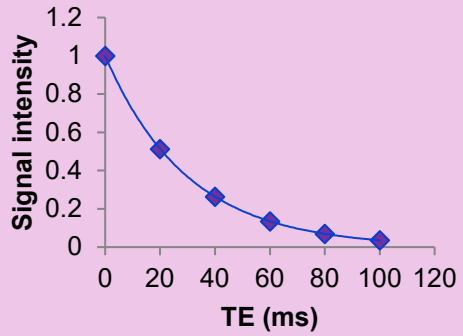
Muscle FF (MRS and MRI)



- Increases with age and DMD disease progression[1–3]
- Muscle FF strongly correlates with function and is predictive of loss of function in DMD[4,5]

Muscle T_2



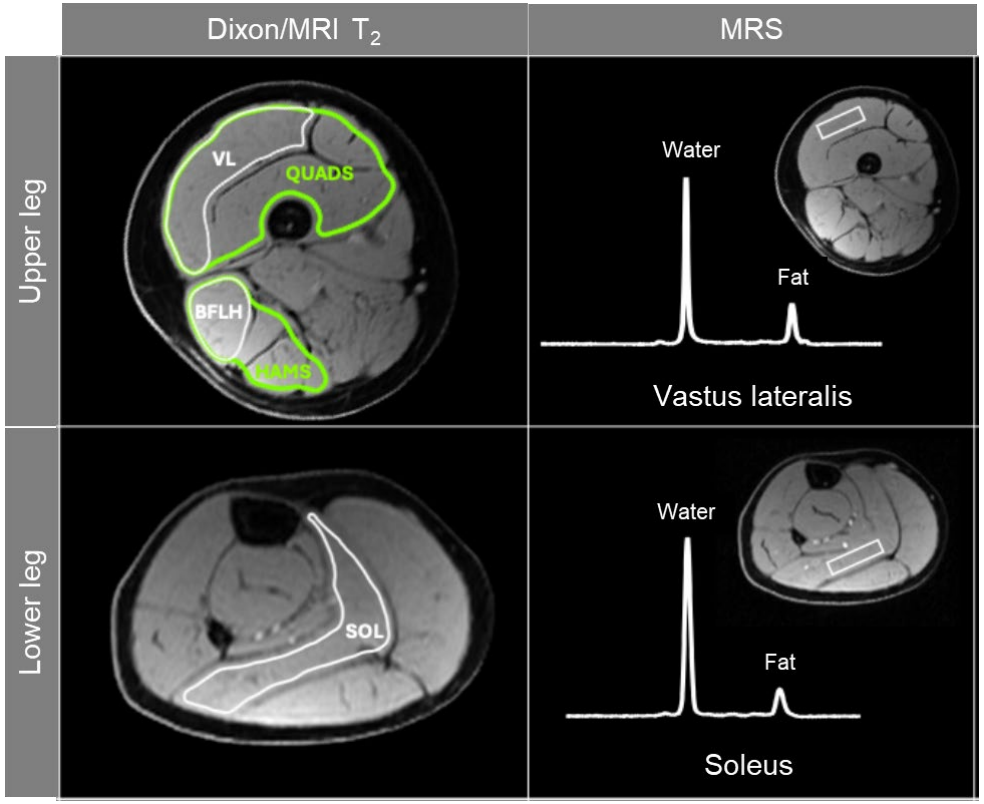


- Elevated in DMD: Increases with increased **FF**, **muscle damage**, **inflammation,** and **edema**[6,7]
- Present even at young ages and when functional assessments are stable, and prior to changes in FF[1,8]

DMD, Duchenne muscular dystrophy; FF, fat fraction; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; T_2, transverse relaxation time; TE, echo time.

1. Willcocks RJ, et al. *Ann Neurol*. 2016; 79:535–547; 2. Willcocks RJ, et al. *JAMA Netw Open*. 2021; 4:e2031851; 3. Rooney WD, et al. *Neurology*. 2020; 94:e1622–e1633; 4. Barnard AM, et al. *Neurology*. 2020; 94:e897–e909; 5. Naarding KJ, et al. *Neurology*. 2020; 94:e1386–e1394; 6. Arpan I, et al. *NMR Biomed*. 2013; 26:320–328; 7. Willcocks RJ, et al. *Neuromuscul Disord*. 2014; 24:393–401; 8. Forbes SC, et al. *PLoS One*. 2014; 9:e106435.

MR methods



- **Localized proton MRS (STEAM)**: Used to measure muscle FF in the soleus and vastus lateralis (muscles critical for lower limb function)
- **Eight-point Dixon MRI**: Used to quantity muscle FF in five pre-selected lower leg muscles/muscle groups important for ambulation (the biceps femoris, hamstring, quadriceps, soleus, and vastus lateralis muscles)
- **Multi-slice spin echo imaging**: Used to create quantitative T_2 maps and mean T_2 values (sensitive to changes in FF and muscle damage, inflammation, and edema) in the same five muscle locations

- A **post hoc global statistical test (Wei-Lachin test)** was applied to evaluate the overall delandistrogene moxeparvovec treatment effect at Week 52 across the different muscle groups and imaging modalities
  - Permutation tests (n=100,000) were stratified within baseline age group to maintain balance between the two treatment arms

FF, fat fraction; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; STEAM, Stimulated Echo Acquisition Mode; T_2, transverse relaxation time.

Patient demographics and baseline clinical characteristics in the EMBARK MR sub-study*

- Demographics and baseline clinical characteristics were comparable between the delandistrogene moxeparvovec and placebo groups
- Steroid use was generally well-balanced between the delandistrogene moxeparvovec and placebo groups

Baseline characteristic	Delandistrogene moxeparvovec† (n=19)	Placebo (n=20)	All (N=39)
Age, mean (SD), years	5.9 (1.10)	6.3 (0.98)	6.1 (1.04)
Dosing weight, mean (SD), kg	22.4 (6.31)	21.8 (5.94)	22.1 (6.05)
Time since corticosteroid treatment started, mean (SD), years	0.8 (0.53)	0.9 (0.51)	0.8 (0.52)
Baseline functional assessment			
NSAA total score, mean (SD), points	23.6 (3.85)	22.4 (3.58)	23.0 (3.71)
TTR, mean (SD), seconds	3.5 (0.98)	3.5 (0.78)	3.5 (0.87)
10MWR, mean (SD), seconds	4.5 (0.60)	5.1 (0.75)	4.8 (0.73)
SV95C, mean (SD), meters/second	1.8 (0.30)	1.8 (0.26)	1.8 (0.28)
100MWR, mean (SD), seconds	56.0 (9.98)	61.6 (18.45)	58.8 (14.91)
Time to ascend 4 steps, mean (SD), seconds	2.8 (0.55)	3.5 (0.92)	3.1 (0.83)

*Only a subset of EMBARK study participants underwent MR assessments. †Administered at a dose of 1.33×10^{14} vg/kg.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; MR, magnetic resonance; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SV95C, Stride Velocity 95th Centile; TTR, Time to Rise.

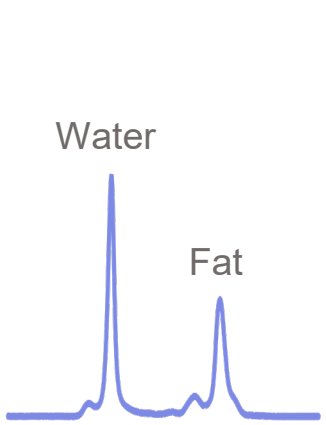
MRS FF, MRI FF, and MRI T_2 were generally balanced at baseline

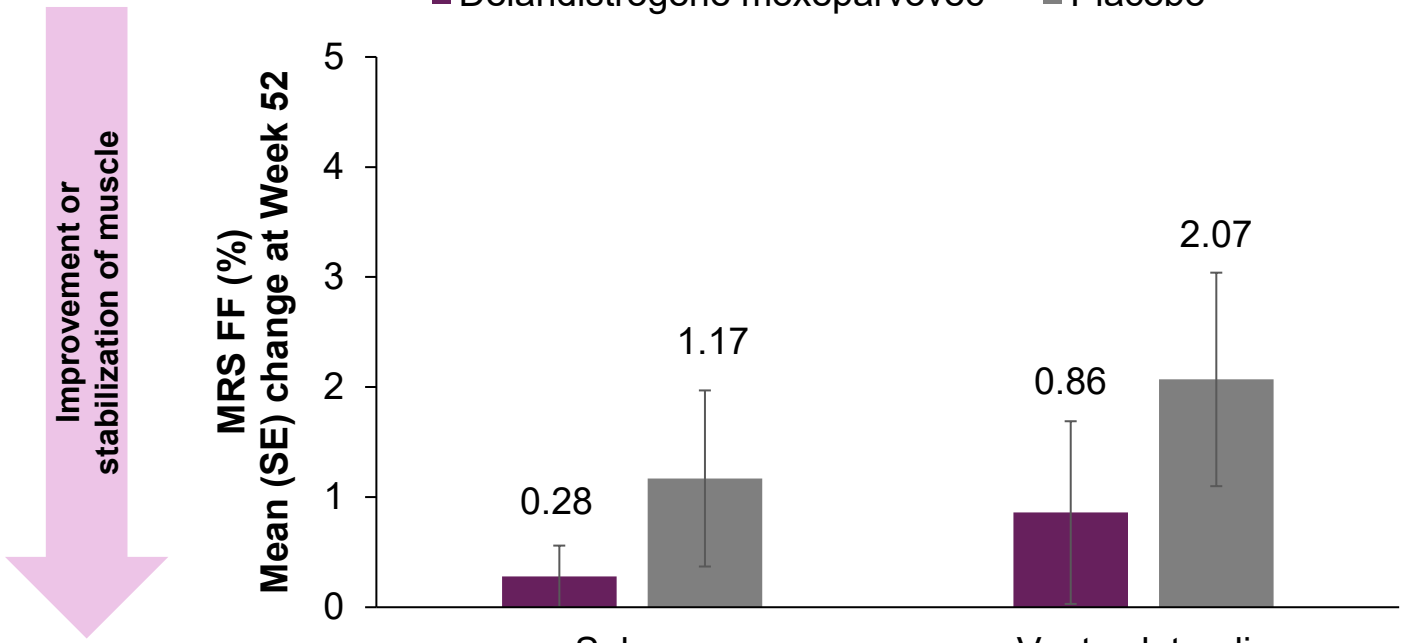
Muscle group	Treatment	MRS FF (%) n Mean (SE)	MRI FF (%) n Mean (SE)	MRI T_2 (msec) n Mean (SE)
Biceps femoris	Delandistrogene moxeparvovec	NA	15 11.0 (0.82)	13 42.3 (0.62)
	Placebo	NA	16 14.9 (3.84)	18 45.6 (1.76)
Hamstring	Delandistrogene moxeparvovec	NA	15 12.9 (0.84)	13 42.8 (0.60)
	Placebo	NA	16 13.6 (1.71)	18 44.4 (1.05)
Quadriceps	Delandistrogene moxeparvovec	NA	15 11.5 (1.09)	13 42.3 (0.89)
	Placebo	NA	16 11.0 (1.77)	18 43.5 (1.02)
Soleus	Delandistrogene moxeparvovec	16 5.7 (0.85)	16 9.3 (0.98)	15 40.5 (0.91)
	Placebo	17 4.4 (0.59)	17 7.6 (0.63)	17 40.8 (0.88)
Vastus lateralis	Delandistrogene moxeparvovec	15 5.5 (0.84)	15 9.9 (1.14)	13 40.9 (0.94)
	Placebo	17 8.6 (2.44)	16 9.8 (1.86)	18 42.4 (1.02)

FF, fat fraction; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, non-applicable; SE, standard error; T_2, transverse relaxation time.

MRS FF (%): Change from baseline to Week 52

Across both muscles, the **delandistrogene moxeparvovec group** had a **smaller increase** in MRS-measured muscle FF than the placebo group



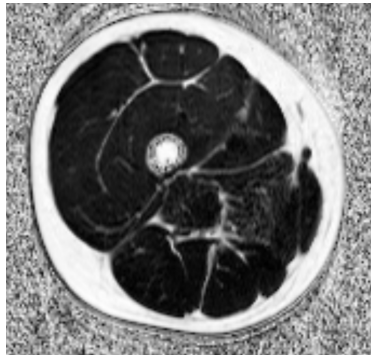


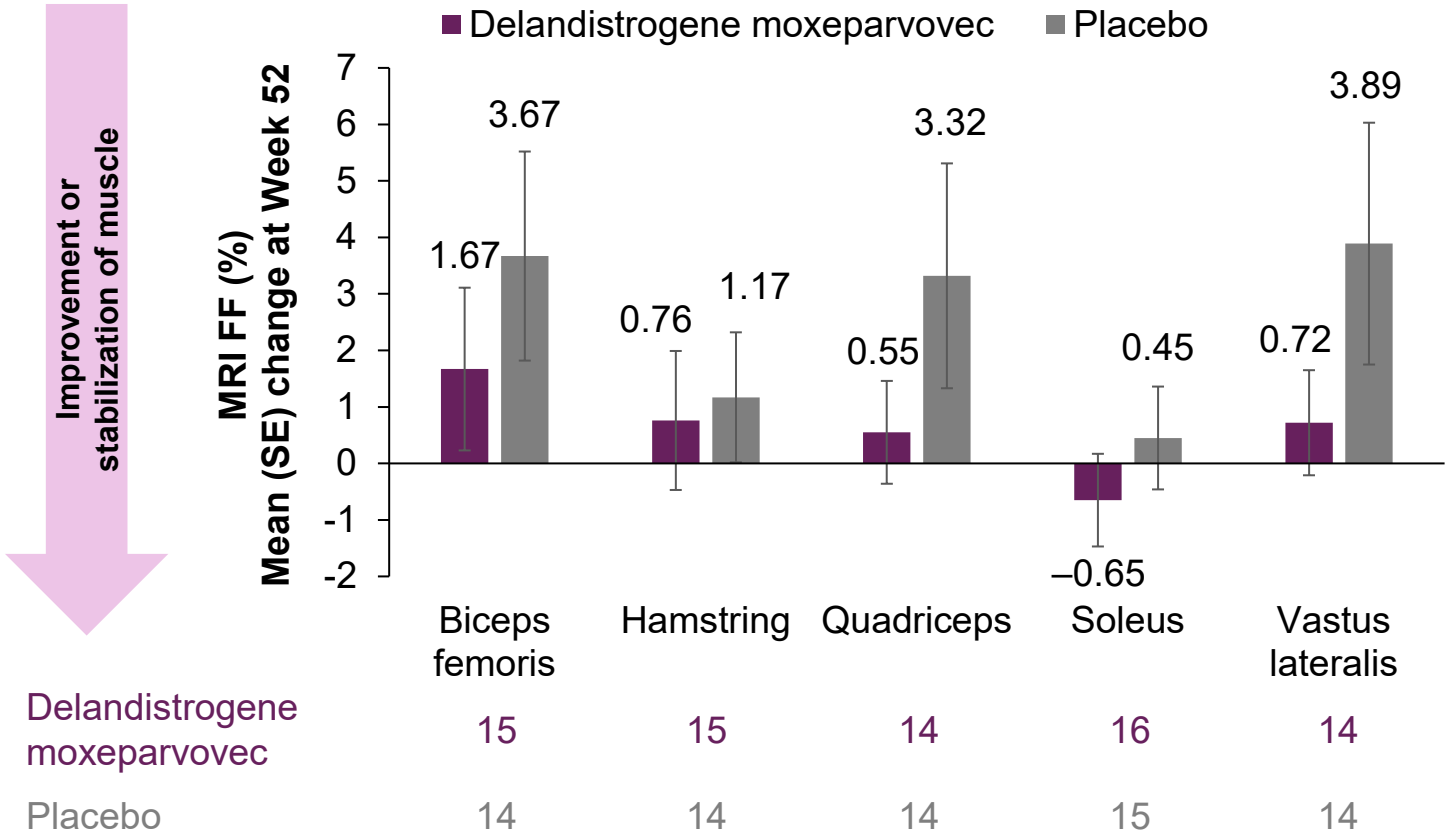
	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	16	13
Placebo	15	15

FF, fat fraction; MRS, magnetic resonance spectroscopy; SE, standard error.

MRI FF (%): Change from baseline to Week 52

The **delandistrogene moxeparvovec group** had **smaller increases** versus the placebo group across all muscles and muscle groups

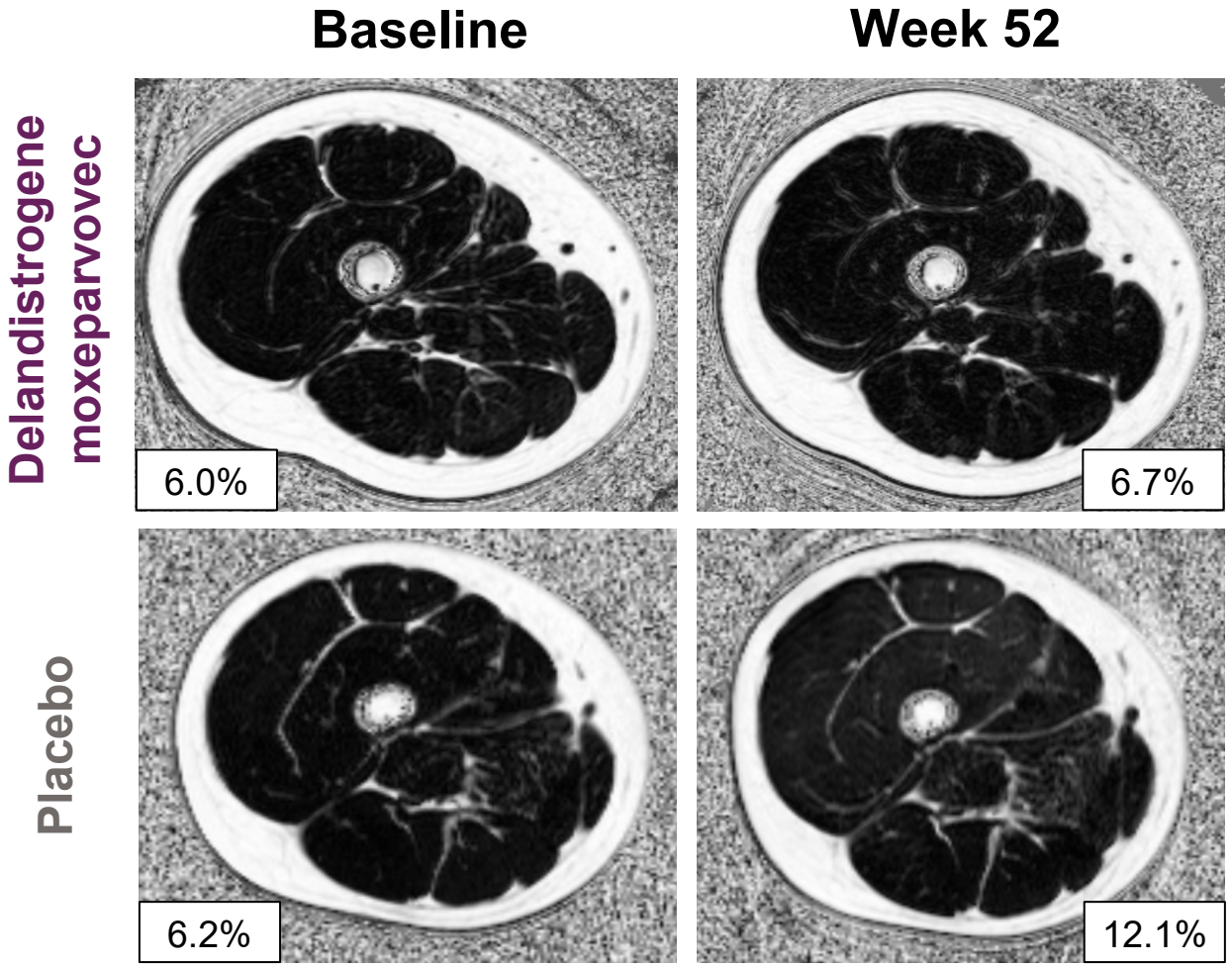




	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	15	15	14	16	14
Placebo	14	14	14	15	14

FF, fat fraction; MRI, magnetic resonance imaging; SE, standard error.

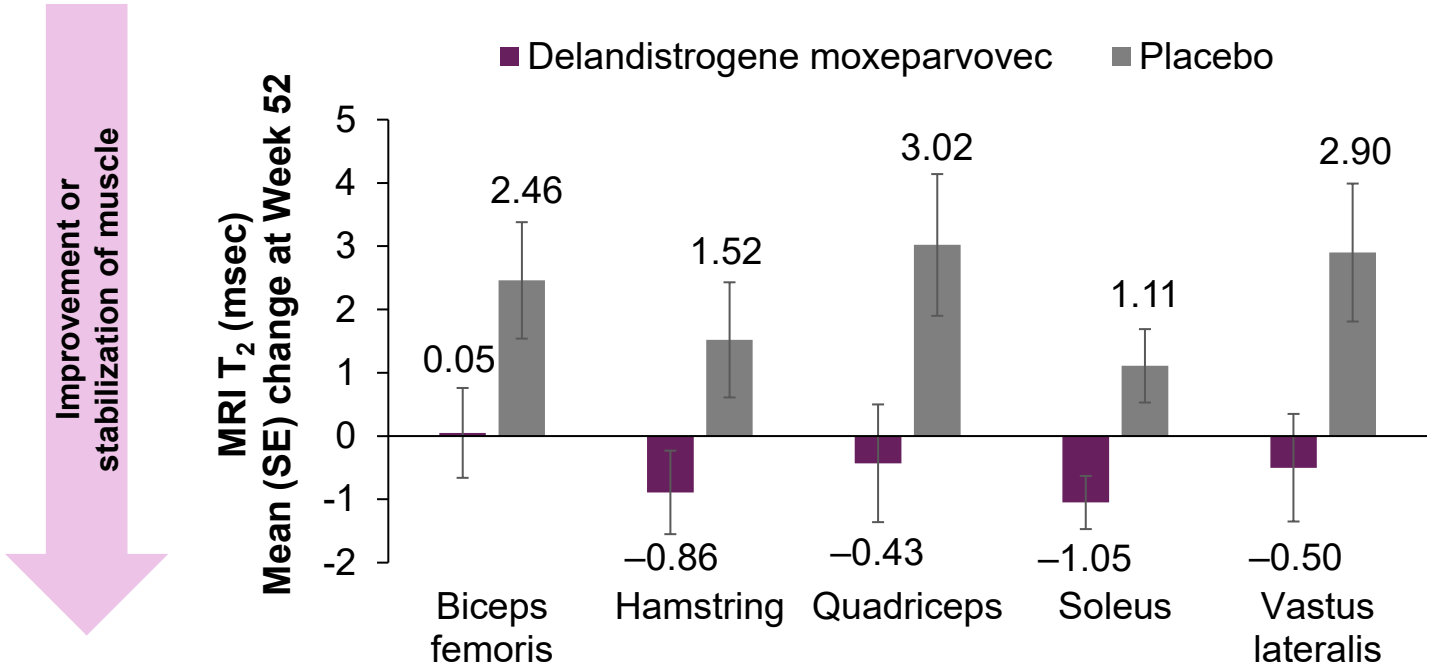
Dixon MRI FF maps of the upper leg at baseline and Week 52 in two patients with similar baseline vastus lateralis FF values



MRI, magnetic resonance imaging; FF, fat fraction.

MRI T_2 (msec): Change from baseline to Week 52

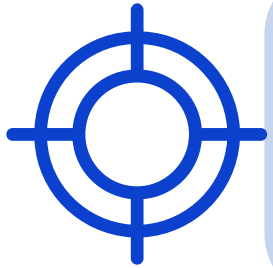
- The **delandistrogene moxeparvovec group** showed a **decrease (improvement)** in T_2 in **four out of five muscles and muscle groups**
- The **placebo group** showed an **increase (worsening)** in T_2 across **all five muscles and muscle groups**



	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	12	12	12	15	12
Placebo	15	15	15	15	15

MRI, magnetic resonance imaging; SE, standard error; T_2, transverse relaxation time.

Global statistical test



The post hoc **global statistical test** to determine the strength of the delandistrogene moxeparvovec treatment effect versus placebo at Week 52 across MR parameters yielded a ***P*-value of 0.0328**, supporting the overall treatment benefit, with stabilization or slowing of disease progression with delandistrogene moxeparvovec across the 12 MR parameters

MR, magnetic resonance.

Conclusions

- Overall, the magnitudes of change in MRS- and MRI-measured FF were **reduced** in the delandistrogene moxeparvovec versus the placebo group at Week 52, **suggesting stabilization or less progression of muscle pathology with treatment**
- In treated patients, MRI T_2 was **reduced** from baseline in **four of the five studied muscle locations**, indicating improvement in muscle integrity; the placebo group showed worsening (T_2 increases) across all studied muscles
- Results of the **global statistical test support the individual MR results** and yielded a nominally statistically significant difference between the delandistrogene moxeparvovec and placebo groups across muscle regions and MR parameters
- Findings suggest that proximal leg muscles are the earliest affected in DMD, consistent with previous reports[1,2]
- Limitations included the small sample size of MR assessments and the exploratory nature of the outcomes
- MR changes were congruent with secondary functional outcomes from EMBARK Part 1 showing stabilization or slowing of disease progression in delandistrogene moxeparvovec-treated patients and progression in placebo-treated patients, demonstrating treatment efficacy[3]
- Additional analyses are underway to quantify signs of continued long-term benefits for muscle pathology

DMD, Duchenne muscular dystrophy; FF, fat fraction; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; T_2, transverse relaxation time.

1. Barnard AM, et al. *PLoS One*. 2018; 13:e0194283; 2. Rooney WD, et al. *Neurology*. 2020; 94:e1622–e1633; 3. Mendell JR, et al. *Nat Med.* 2025; 31:332–341.

Additional EMBARK presentations at MDA

- Poster P168: Muscle MRI Outcomes in Patients with Duchenne Muscular Dystrophy Treated with Delandistrogene Moxeparvovec: Findings from EMBARK Part 1
  - K Vandenborne, G Walter, V Straub, R Willcocks, S Forbes, S Ennamuri, K Ding, C Reid, AP Murphy, M Manfrini, JS Elkins, LR Rodino-Klapac

- Poster P169: Long-Term Functional Outcomes, Safety, and Micro-Dystrophin Expression Following Delandistrogene Moxeparvovec Treatment in DMD: EMBARK 2-Year Results
  - JR Mendell, F Muntoni, CM McDonald, E Mercuri, E Ciafaloni, H Komaki, C Leon-Astudillo, A Nascimento, C Proud, U Schara-Schmidt, A Veerapandiyan, C Zaidman, M Furgerson, K Ding, P Singh, R Potter, D Asher, AP Murphy, C Reid, G Hooper, C Torre, M Manfrini, JS Elkins, LR Rodino-Klapac on behalf of the EMBARK Study Group

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