Muscle MRI outcomes in patients with Duchenne Muscular Dystrophy treated with delandistrogene moxeparvovec: Findings from EMBARK Part 1

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*Presenting on behalf of the author group (email address: medinfo@sarepta.com)

Disclosures

- Krista Vandenborne was supported by a research service agreement between the University of Florida and Sarepta Therapeutics, Inc.

Background

- **Duchenne muscular dystrophy** (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 stabilise or slow disease progression in DMD[4–7]
  - It is approved in the US and in other select countries[8–14]

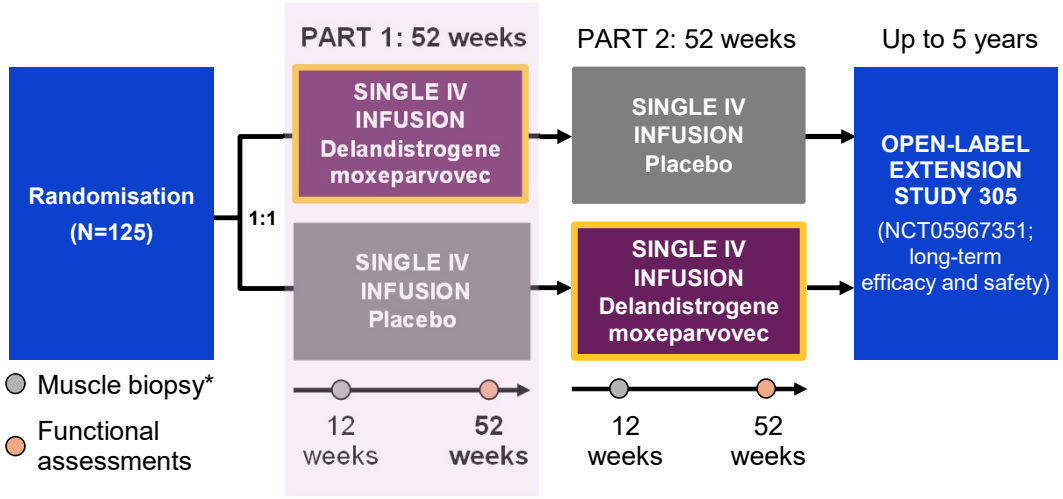
- Part 1 of the **Phase 3, randomised, placebo-controlled EMBARK trial** of delandistrogene moxeparvovec in ambulatory patients with DMD aged ≥4 to <8 years is completed; the primary endpoint of change from baseline to Week 52 in NSAA was not met[7,15]
  - However, multiple secondary functional endpoints showed stabilisation of DMD disease progression and a manageable safety profile, consistent with early-phase trials[6,7,16–18]

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

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. *Methods Mol Biol*. 2008; 434:205–219; 6. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131; 7. Mendell JR, et al. Presented at MDA 2024; Poster M164; 8. US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information (Accessed October 2024); 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; 15. ClinicalTrials.gov. NCT05096221 (Accessed October 2024); 16. Mendell JR, et al. *Muscle Nerve*. 2024; 69:93–98; 17. Mendell JR, et al. *Front Cell Dev Biol*. 2023; 11:1167762; 18. Zaidman CM, et al. *Ann Neurol*. 2023; 94:955–968.

EMBARK study design



Stratification was based on age at randomisation (≥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 randomisation
- 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 titres <1:400

Exploratory magnetic resonance endpoints

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

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

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

- Cardiac MRI endpoints from EMBARK are shared in a separate WMS presentation[1]

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

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

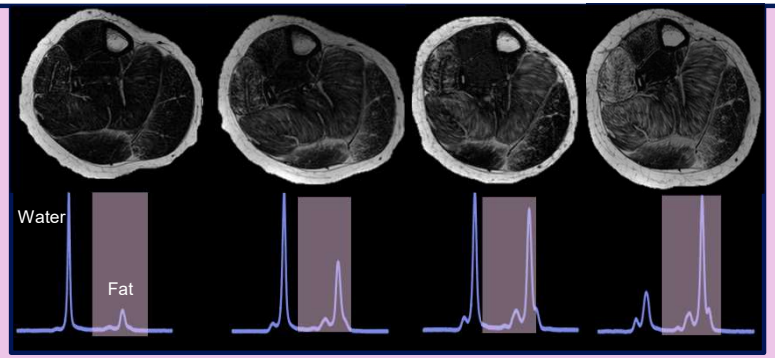
Magnetic resonance exploratory endpoints

Magnetic resonance (MR) is a non-invasive method to monitor DMD disease progression

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

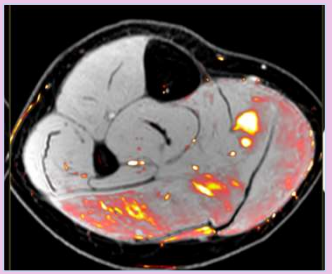
EMBARK MR endpoints included biomarkers of muscle health

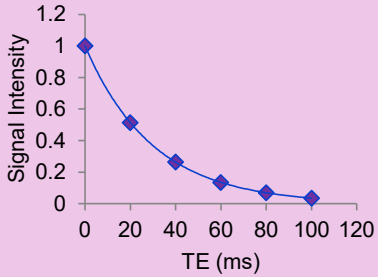
Muscle fat fraction (MRS and MRI)



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

Muscle T_2



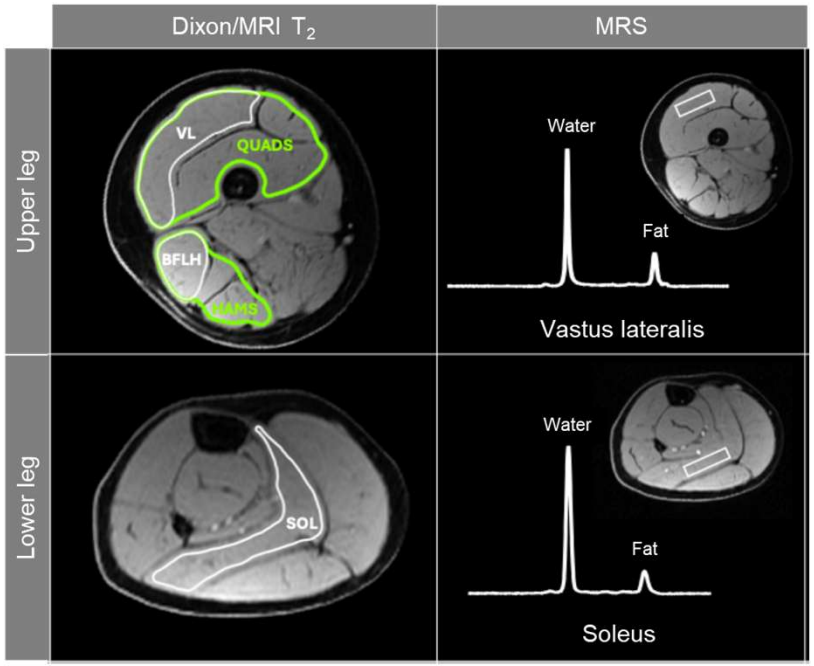


- Elevated in DMD: Increases with increased **fat fraction**, muscle **damage**, **inflammation** and **oedema**[6,7]
- Present even at young ages and when functional assessments are stable, and prior to changes in fat fraction[8,9]

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

1. Willcocks RJ, et al. *Ann Neurol*. 2016; 79(4):535–547; 2. Willcocks RJ, et al. *JAMA Netw Open*. 2021;4(1):e2031851; 3. Rooney WD, et al. *Neurology*. 2020;94(15):e1622–e1633; 4. Barnard et al. *Neurology*. 2020;94(9):e897–e909; 5. Naarding KJ, et al. *Neurology*. 2020;94(13):e1386–e1394; 6. Arpan et al. *NMR Biomed*. 2013;26(3):320–328. 7. Willcocks RJ, et al. *Neuromuscul Disord*. 2014;24(5):393–401; 8. Forbes et al, *PLoS One*. 2014 Sep 9;9(9):e106435. 9. Willcocks RJ, et al. *Ann Neurol.* 2016;79(4):535–547.

Magnetic resonance methods



- **Localised proton MRS (STEAM)**: **muscle fat fraction** in the **soleus and vastus lateralis** (muscles critical for lower limb function)
- **Eight-point Dixon MRI**: **muscle fat fraction** in five preselected lower leg muscles/muscle groups important for ambulation (the **biceps femoris, hamstring, quadriceps, soleus and vastus lateralis muscles**)
- **Multi-slice spin echo imaging**: **quantitative T_2 maps** and **mean T_2 values** (sensitive to changes in fat fraction and muscle damage, inflammation and oedema) 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** 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

DMD, Duchenne muscular dystrophy; 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 generally comparable between the delandistrogene moxeparvovec and placebo groups

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)
4–5 years, n (%)	10 (52.6)	9 (45.0)	19 (48.7)
6–7 years, n (%)	9 (47.4)	11 (55.0)	20 (51.3)
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), metres/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.
10MWR, 10-metre Walk/Run; 100MWR, 100-metre Walk/Run; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SV95C, Stride Velocity 95th Centile; TTR, Time to Rise.

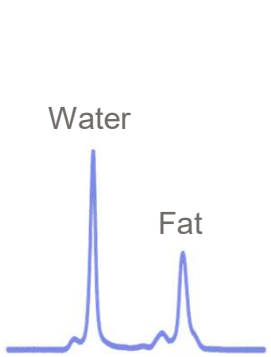
MRS FF, MRI FF and MRI T_2 were generally balanced at baseline

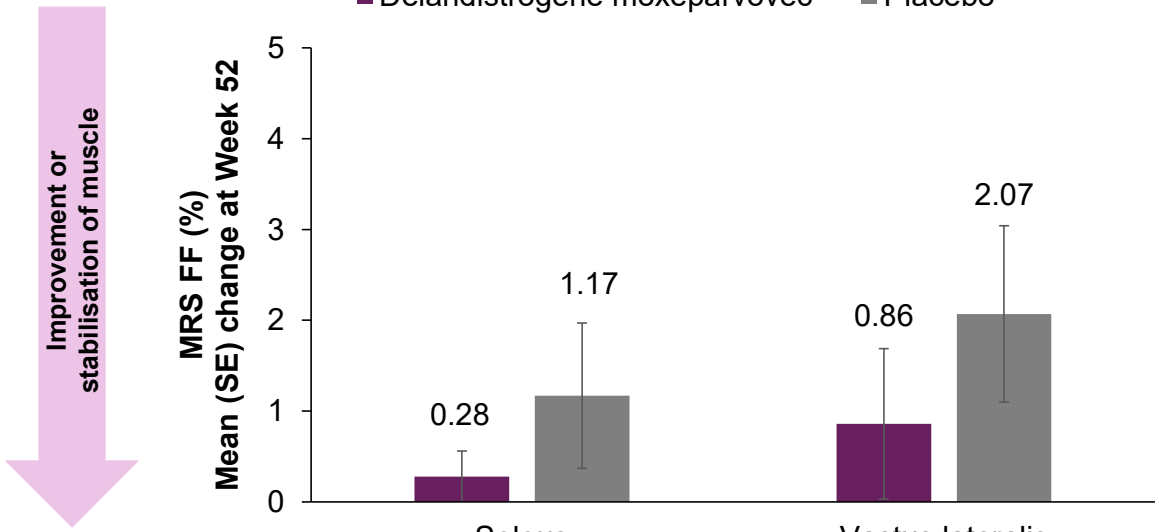
Muscle group	Treatment	MRS FF (%) n Mean (SE)	MRI FF (%) n Mean (SE)	MRI T_2 (msec) n Mean (SE)
Biceps femoris	Delandistrogene moxeparvovec	NA	15 11.0 (0.82)	13 42.3 (0.62)
	Placebo	NA	16 14.9 (3.84)	18 45.6 (1.76)
Hamstring	Delandistrogene moxeparvovec	NA	15 12.9 (0.84)	13 42.8 (0.60)
	Placebo	NA	16 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; n, number; SE, standard error; T_2, transverse relaxation time.

Change from baseline to Week 52 in MRS fat fraction (%)

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



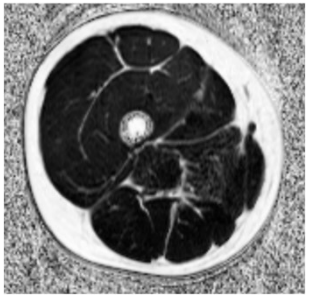


	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	16	13
Placebo	15	15

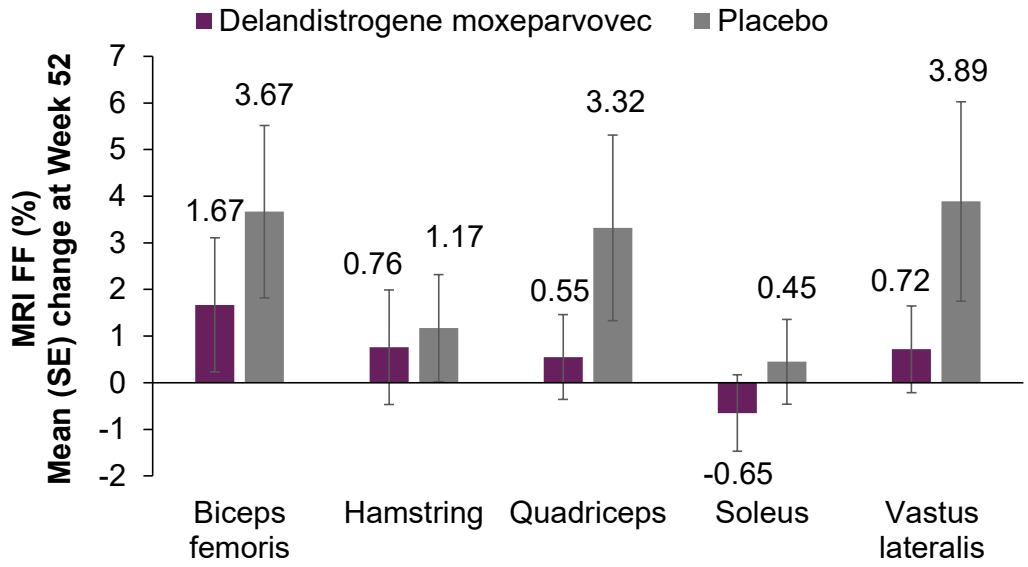
FF, fat fraction; MRS, magnetic resonance spectroscopy; SE, standard error.

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

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



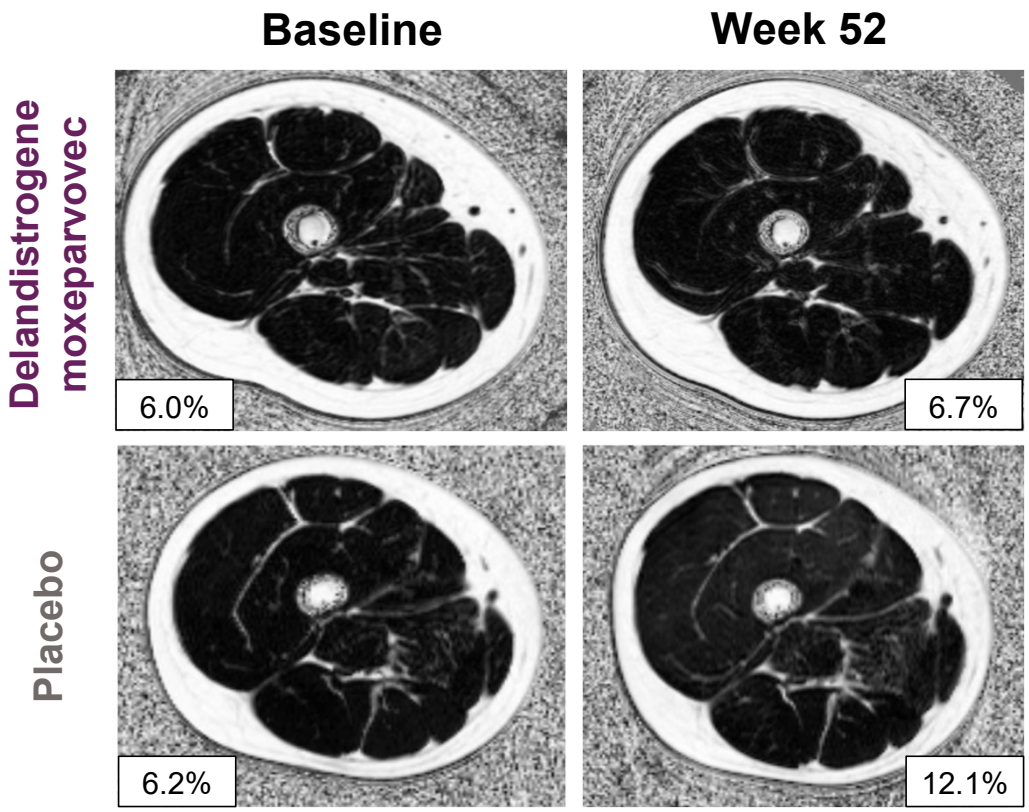
Improvement or stabilisation of muscle



	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 fat fraction maps of the upper leg at baseline and Week 52 in two patients with similar baseline VL FF values

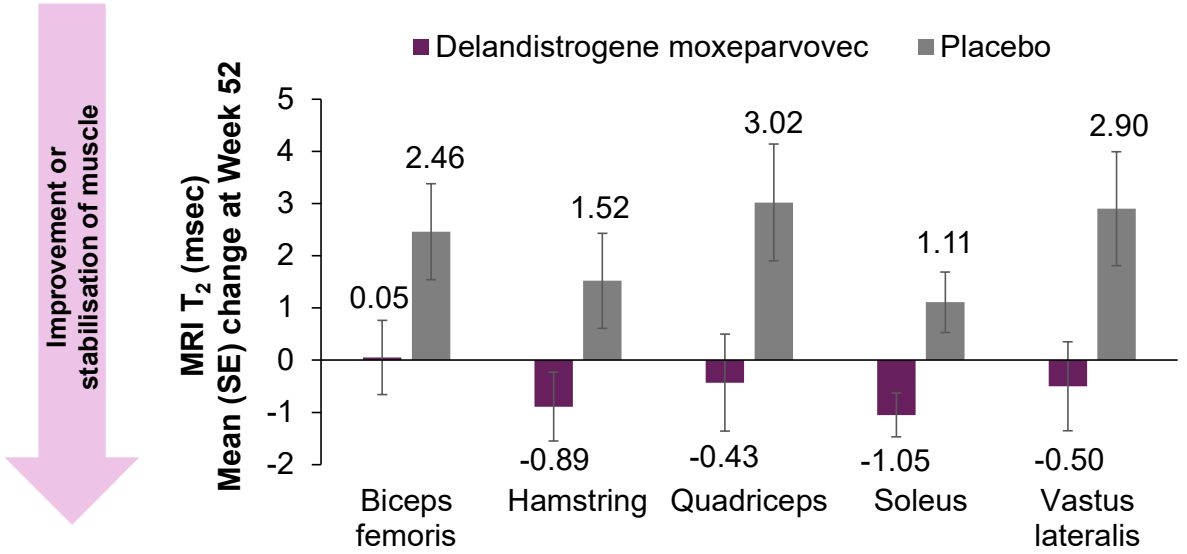


FF, fat fraction; VL, vastus lateralis.

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

The **delandistrogene moxeparvovec group** showed a **decrease (improvement)** in T_2 in **4 out of 5 muscles and muscle groups**

The **placebo group** showed an **increase (worsening)** in T_2 across **all 5 muscles and muscle groups**



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

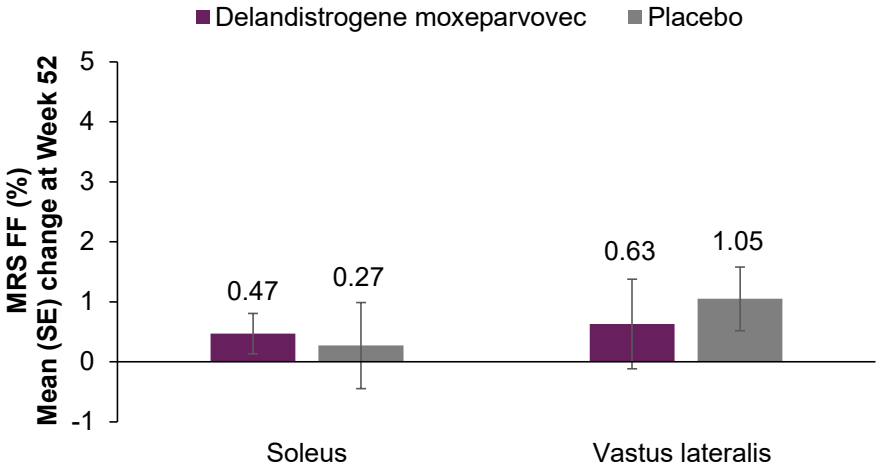
MRI, magnetic resonance imaging; SE, standard error; T_2, transverse relaxation time.

Change from baseline to Week 52 in MRS fat fraction (%) by age subgroup

In the **6–7-year-old age subgroup**, the **delandistrogene moxeparvovec** group had **smaller increases** in MRS-measured fat fraction in both muscles compared with the placebo group

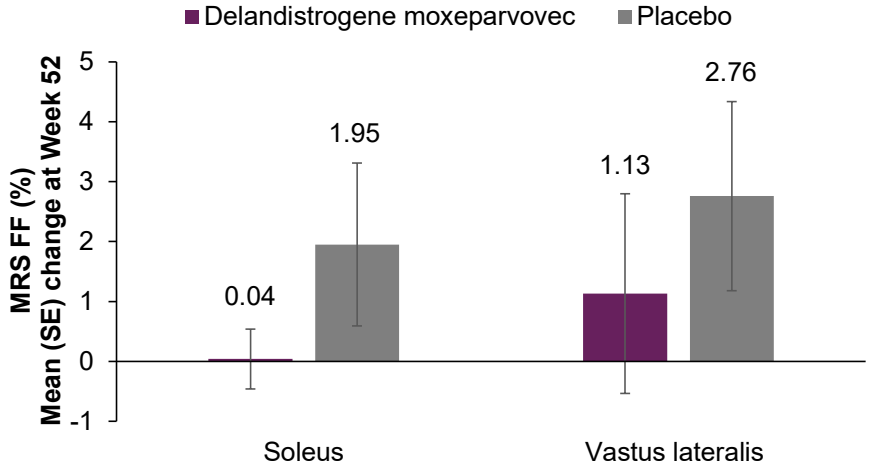
Improvement or stabilisation of muscle

4- to 5-year-old age subgroup



	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	9	7
Placebo	7	6

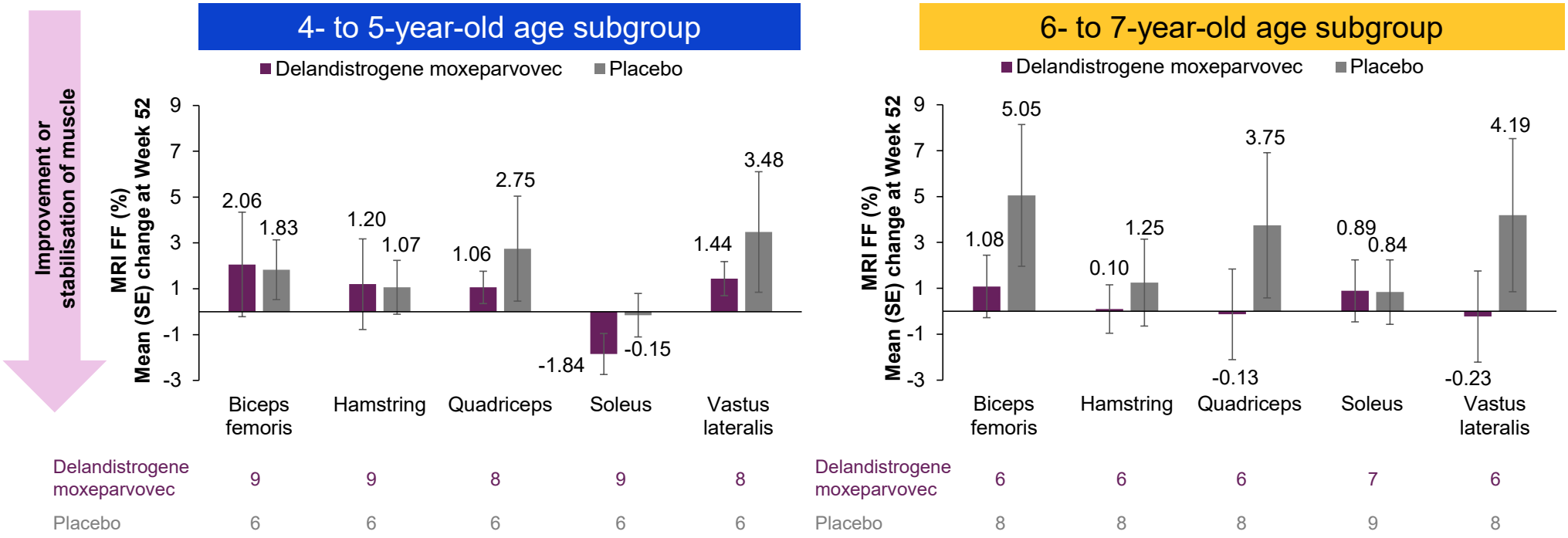
6- to 7-year-old age subgroup



	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	7	6
Placebo	8	9

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

Change from baseline to Week 52 in MRI fat fraction (%) by age subgroup



4- to 5-year-old age subgroup	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	9	9	8	9	8
Placebo	6	6	6	6	6

6- to 7-year-old age subgroup	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	6	6	6	7	6
Placebo	8	8	8	9	8

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

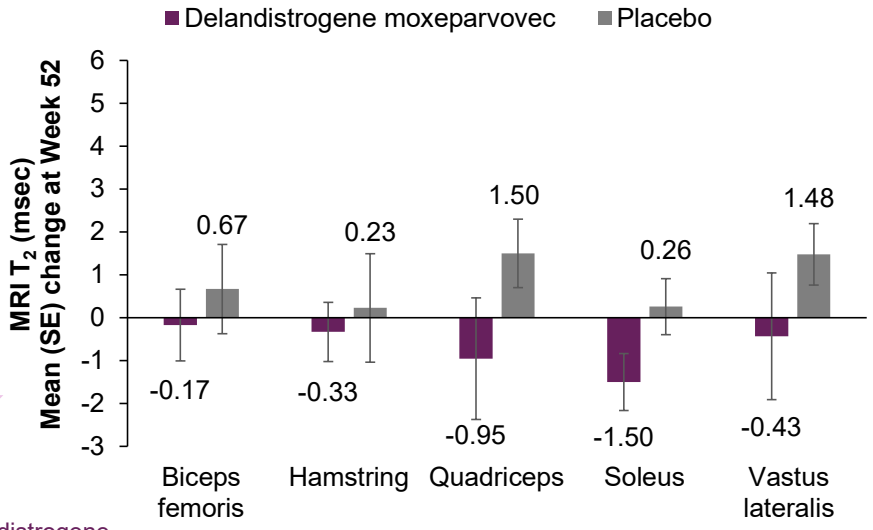
Change from baseline to Week 52 in MRI T_2 (msec) by age subgroup

The **delandistrogene moxeparvovec group** showed a **decrease (improvement)** in T_2 in **all muscles and muscle groups** in the **4–5-year-old subgroup** and in **3 out of 5** muscle locations in the **6–7-year-old subgroup**

The **placebo group** showed an **increase (worsening)** across **all 5 muscle locations** in **both age subgroups**

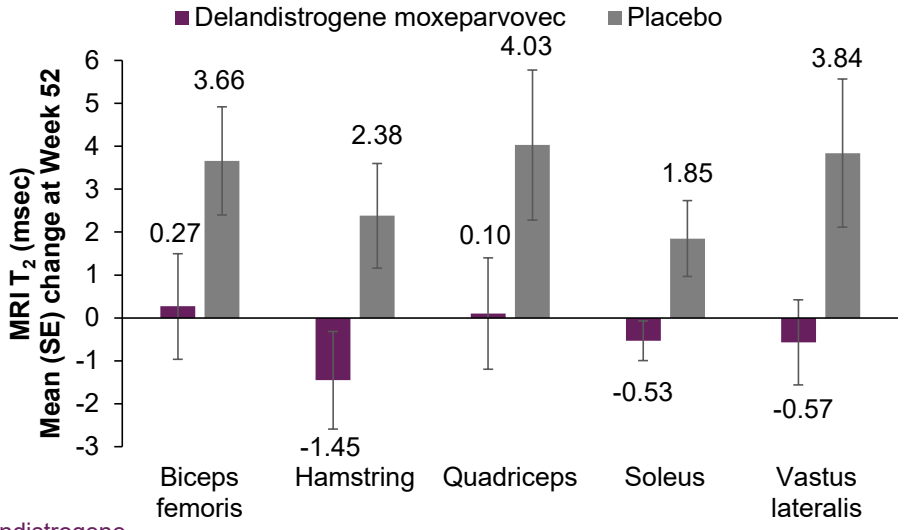
Improvement or stabilisation of muscle

4- to 5-year-old age subgroup



	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	6	6	6	8	6
Placebo	6	6	6	7	6

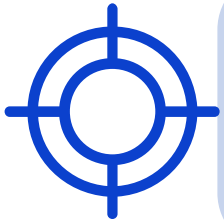
6- to 7-year-old age subgroup



	Biceps femoris	Hamstring	Quadriceps	Soleus	Vastus lateralis
Delandistrogene moxeparvovec	6	6	6	7	6
Placebo	9	9	9	8	9

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 across MR parameters yielded a ***P*-value of 0.0328**, supporting the overall treatment benefit, with stabilisation 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 stabilisation or less progression of muscle pathology with treatment**
- In treated patients, MRI T_2 was **reduced** from baseline in **4 of the 5 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 stabilisation or slowing of disease progression in delandistrogene moxeparvovec-treated patients and progression in placebo-treated patients, demonstrating treatment efficacy[3]
  - Whilst EMBARK Part 1 did not meet the primary endpoint, multiple secondary functional endpoints showed stabilisation of DMD disease progression, and a manageable safety profile was observed

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. Presented at MDA 2024; Poster #M164.

Additional EMBARK presentations at WMS

- Safety and efficacy of delandistrogene moxeparvovec versus placebo in Duchenne Muscular Dystrophy: Phase 3 EMBARK primary results
  - JR Mendell, F Muntoni, CM McDonald, EM Mercuri, E Ciafaloni, H Komaki, C Leon-Astudillo, A Nascimento, C Proud, U Schara-Schmidt, A Veerapandiyan, CM Zaidman, AP Murphy, C Reid, DR Asher, E Darton, S Mason, P Fontoura, JS Elkins, LR Rodino-Klapac, on behalf of the EMBARK Study Group

- Cardiac MRI outcomes in patients with Duchenne Muscular Dystrophy treated with delandistrogene moxeparvovec: Findings from EMBARK Part 1
  - G Walter, K Vandenborne, J Bourke, J Soslow, S Mason, E Palatinsky, C Wandel, K Ding, C Reid, AP Murphy, M Manfrini, J Richardson, JS Elkins

MRI, magnetic resonance imaging.

Acknowledgements

- The authors thank the patients and their families for their participation in EMBARK, as well as the investigators and trial staff involved in EMBARK
- This study was sponsored by Sarepta Therapeutics, Inc., Cambridge, MA, USA and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland
- Medical writing and editorial support was provided by Leo Mahachi, PhD, and Jen Ciarochi, PhD, of Nucleus Global, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and was funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland