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

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Background

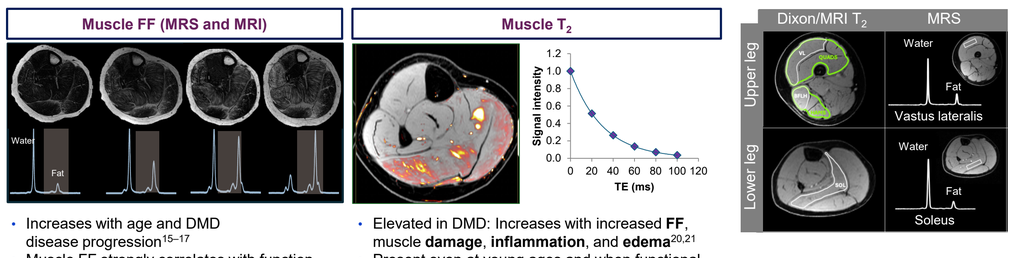
- DMD is a rare, X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in the absence of functional dystrophin[1]
- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy that delivers a transgene encoding an engineered, functional form of dystrophin shown to stabilize or slow disease progression in DMD[2–5]
  - It is approved in the USA and in other select countries[6–13]
- One-year functional and safety data from the Phase 3 EMBARK trial of delandistrogene moxeparvovec in ambulatory patients with DMD (aged ≥4 to <8 years) have been published[2,14]

Objective

- We present pre-specified, exploratory analyses from EMBARK Part 1-treated patients of muscle health and changes in muscle pathology assessed by MR to evaluate the effect of delandistrogene moxeparvovec on DMD disease progression

Methods

Figure 1. EMBARK MR exploratory endpoints



- Increases with age and DMD disease progression[15–17]
- Muscle FF strongly correlates with function and is predictive of loss of function in DMD[18,19]

- Elevated in DMD: Increases with increased **FF**, muscle **damage**, **inflammation**, and **edema**[20,21]
- Present even at young ages and when functional assessments are stable, and prior to changes in FF[16,22]

- MR is a non-invasive method to monitor DMD disease progression that is sensitive to subclinical disease progression and not dependent on patient growth, maturation, or motivation
- **Localized proton MRS (STEAM)** was used to measure muscle FF in the soleus and vastus lateralis (muscles critical for lower limb function)
- **Eight-point Dixon MRI** was used to quantify 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** was used to create quantitative T_2 maps and measure 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

Results

Table 1. Baseline characteristics and functional assessments in the EMBARK MR sub-study were generally comparable between 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)

*Administered at a dose of 1.33×10^{14} vg/kg.

- 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

Results (continued)

Table 2. Baseline MRS FF, MRI FF, and MRI T_2 were generally balanced across muscle groups

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)

Figure 2A. Change from baseline to Weeks 52 and 104 in MRI FF (%)

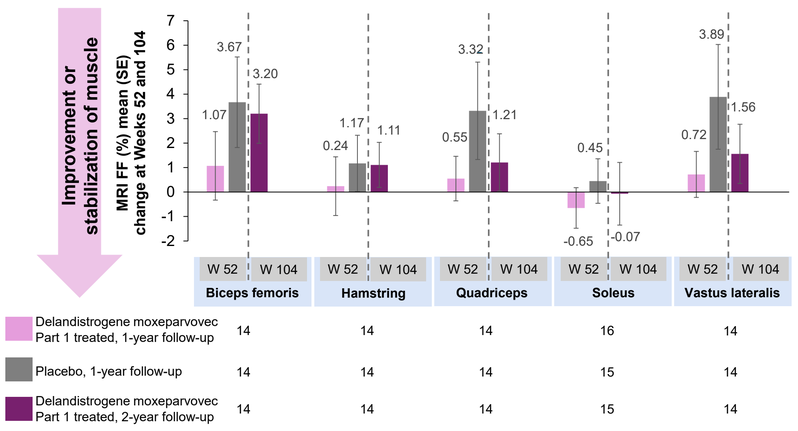
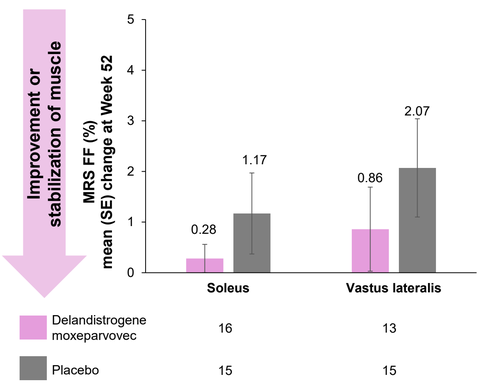


Figure 2B. Change from baseline to Week 52 in MRS FF (%)



- **MRI-measured FF:** At Week 52, the delandistrogene moxeparvovec group had smaller increases versus the placebo group across all muscles (**Figure 2A**)
  - At Week 104, FF remained comparable or lower than observed with placebo at Week 52 (**Figure 2A**)
- **MRS-measured FF:** At Week 52, across both muscles, the delandistrogene moxeparvovec group had a smaller increase in MRS-measured muscle FF than the placebo group (**Figure 2B**)
- Additional analyses are underway to provide a complete assessment of all Week 104 MR outcomes and to contextualize results with an EC cohort

Figure 3. Dixon MRI FF maps of the upper leg at baseline and Week 52

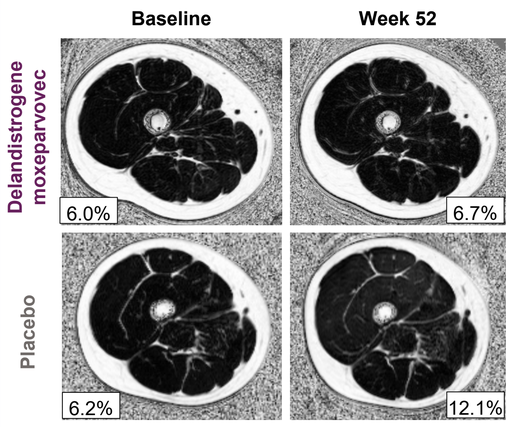
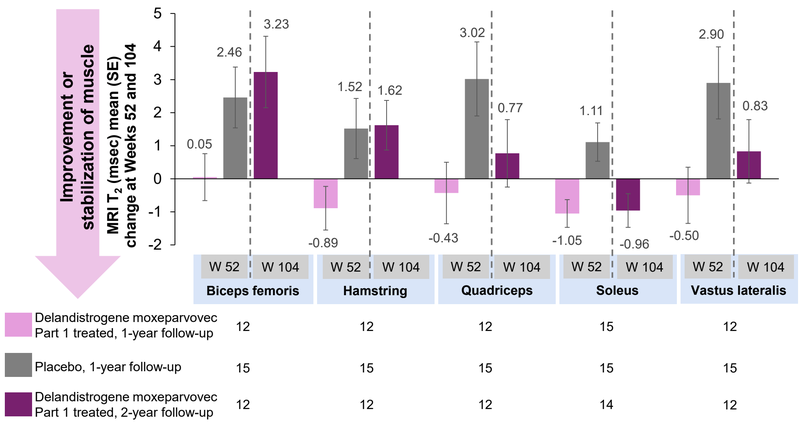


Figure 4. Change from baseline to Weeks 52 and 104 in T_2 (msec)



- An example **Dixon MRI FF map** of the upper leg at baseline and Week 52 in one delandistrogene moxeparvovec-treated patient and one placebo-treated patient with similar baseline vastus lateralis FF values are shown in **Figure 3**
- **MRI-measured T_2:** At Week 52, the delandistrogene moxeparvovec group showed improvement across four of the five muscles and muscle groups versus worsening in the placebo group across all five muscle groups (**Figure 4**)
  - At Week 104, three (quadriceps, soleus, vastus lateralis) of the five muscle groups showed improvement or slowed progression in T_2 in the treated group versus placebo at Week 52
- Additional analyses are underway to provide a complete assessment of all Week 104 MR outcomes and to contextualize results with an EC cohort

Conclusions

- At Week 52, MR measures were improved in the delandistrogene moxeparvovec group compared with placebo group, suggesting stabilization or less progression of muscle pathology with treatment
- Results of the global statistical test at Week 52 support the overall treatment benefit, with stabilization or slowing of disease progression with delandistrogene moxeparvovec across the 12 MR parameters
- At Week 104, MRI changes from baseline generally favored delandistrogene moxeparvovec versus Week 52 placebo, even though some degree of progression of muscle pathology was observed
- Additional analyses are underway to quantify signs of continued long-term benefits for muscle pathology
- Findings suggest that proximal leg muscles are the earliest affected in DMD, consistent with previous reports[2,3]

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Abbreviations

10MWR,10-meter Walk/Run; 100MWR, 100-meter Walk/Run; DMD, Duchenne muscular dystrophy; EC, external control; FF, fat fraction; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, not available; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SD, standard deviation; SE, standard error; STEAM, Stimulated Echo Acquisition Mode; SV95C, Stride Velocity 95th Centile; T_2, transverse relaxation time; TE, echo time; TTR, Time to Rise; W, week.

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