Clinical Validation of the Association Between Micro-Dystrophin Expression and Muscle MRI with Functional Outcomes: A Pooled Analysis of Patients with Duchenne Muscular Dystrophy Treated with Delandistrogene Moxeparvovec

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Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene therapy that delivers a transgene encoding micro-dystrophin, an engineered, functional form of dystrophin shown to slow disease progression in patients with DMD[1–4]
- The delandistrogene moxeparvovec mechanism of action targets the underlying cause of DMD, the absence of functional dystrophin, to restore muscle cell stability and slow functional decline
- Delandistrogene moxeparvovec is approved in the US and in other select countries for the treatment of ambulatory patients with DMD who have a confirmed *DMD* mutation[5,6]
- There is a need to understand the correlation of both delandistrogene moxeparvovec micro-dystrophin expression and skeletal muscle MRI fat fraction (FF) outcomes with functional efficacy outcomes following delandistrogene moxeparvovec treatment
  - Understanding such relationships could further support the use of micro-dystrophin expression as a biomarker and skeletal muscle MRI as a non-invasive biomarker to monitor disease progression and treatment response in DMD

Objective

- To report correlations of micro-dystrophin expression and skeletal muscle MRI FF with functional outcomes using pooled data from clinical studies of delandistrogene moxeparvovec in patients with DMD

Methods

- Data were pooled from subsets of ambulatory patients from Study 102 (NCT03769116; ambulatory patients aged ≥4 to <8 years),[7] ENDEAVOR (NCT04626674; multiple cohorts of ambulatory and non-ambulatory patients),[8] and EMBARK (NCT05096221; ambulatory patients aged ≥4 to <8 years)[9] (**Table 1**)
- Correlation of changes in functional outcomes (NSAA, TTR, 10MWR, 100MWR, and 4SC) with delandistrogene moxeparvovec micro-dystrophin expression (western blot at Week 12) was measured at 1 and 2 years post-infusion*
- Correlation of functional outcomes (NSAA, TTR, 10MWR, 100MWR, and 4SC) with skeletal muscle MRI FF was measured at 1 and 2 years post-infusion*
- For patients in Study 102 and EMBARK who crossed over from placebo to delandistrogene moxeparvovec, two separate changes were calculated: one for the placebo treatment period and another for the delandistrogene moxeparvovec treatment period; the analyses presented here are of the delandistrogene moxeparvovec treatment period
- Pearson correlation coefficients were calculated to assess the relationship between micro-dystrophin expression and functional outcomes, and skeletal muscle MRI FF and functional outcomes

*For Study 102, the study periods were 48-weeks long but were approximated to 1 year (Week 48 approximated to Year 1 and Week 96 approximated to Year 2).

Table 1 *Patients included in the correlation analyses*[7–9]

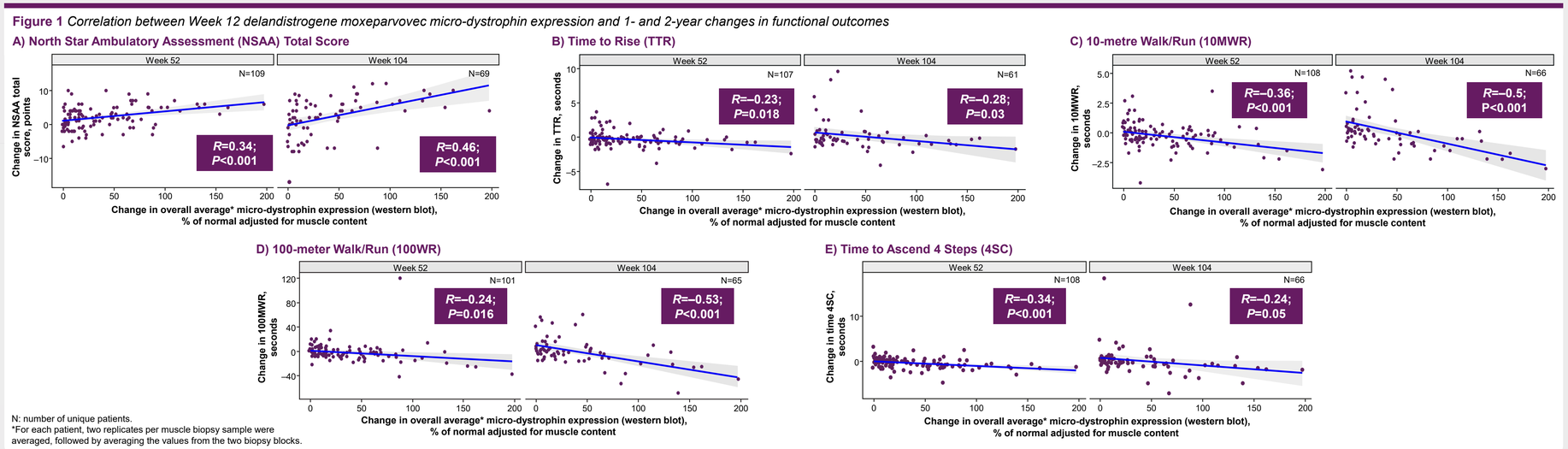
Study, Phase	Study design, N	Population for analysis of correlation of micro-dystrophin expression with functional efficacy*	Population for analysis of correlation of MRI fat fraction with functional efficacy*
Study 102,† **Phase 2**	Randomized, double-blind, placebo-controlled, crossover study (all patients received delandistrogene moxeparvovec in either Part 1 or Part 2); N=41	Ambulatory patients with DMD aged ≥4 to <8 years (N=40)	Ambulatory patients with DMD aged ≥4 to <8 years (N=7)
ENDEAVOR,‡ **Phase 1b**	Open-label study, eight cohorts; N=83	Ambulatory patients with DMD (N=39) • Cohort 1: ≥4 to <8 years (n=20) • Cohort 2: ≥8 to <18 years (n=6) • Cohort 4: ≥3 to <4 years (n=7) • Cohort 5A: ≥4 to <9 years (n=6)	Ambulatory patients with DMD (N=3) • Cohort 2: ≥8 to <18 years (n=1) • Cohort 5A: ≥4 to <9 years (n=2)
EMBARK,§ **Phase 3**	Randomized, double-blind, placebo-controlled, crossover study (all patients received delandistrogene moxeparvovec in either Part 1 or Part 2); N=125	Ambulatory patients with DMD aged ≥4 to <8 years (N=32)	Ambulatory patients with DMD aged ≥4 to <8 years (N=38)

*Populations reflect those used in the Year 1 pooled analysis and may differ from the original study populations based on data availability for the correlation analyses; sample sizes may differ for the Year 2 analysis. †NCT03769116. ‡NCT04626674. §NCT05096221.

Results

- Statistically significant correlations were observed between Week 12 micro-dystrophin expression and both 1- and 2-year functional outcomes, with correlations increasing from Year 1 to Year 2, demonstrating a durable treatment effect (**Figure 1**)
  - Some patients with low micro-dystrophin expression showed changes in NSAA total score comparable to those observed in patients with high expression
- The correlation between Week 12 micro-dystrophin expression and 1- and 2-year functional outcomes was also assessed in patients in the placebo group of Study 102 and EMBARK; no correlation was observed
- Variability in functional outcomes was high, but remained consistent with the range observed in the placebo group

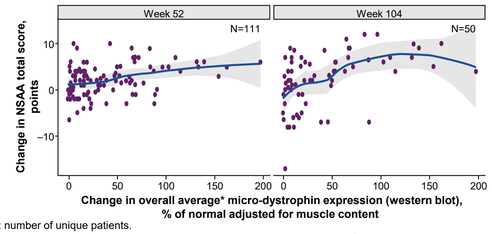
Figure 1 *Correlation between Week 12 delandistrogene moxeparvovec micro-dystrophin expression and 1- and 2-year changes in functional outcomes*



N: number of unique patients.
*For each patient, two replicates per muscle biopsy sample were averaged, followed by averaging the values from the two biopsy blocks.

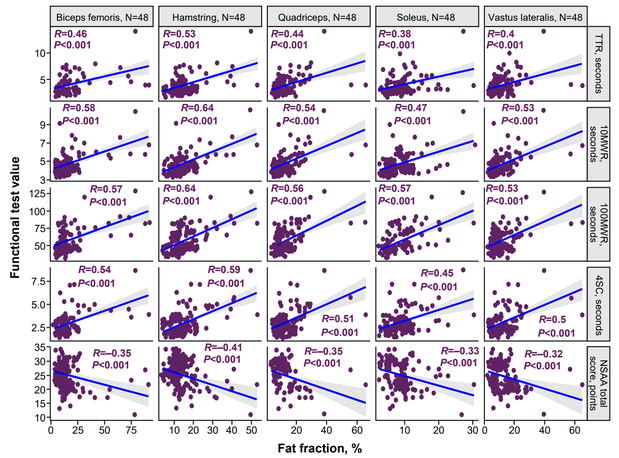
- Smoothing curves (LOESS) were fit to Week 12 micro-dystrophin expression versus changes in NSAA total score at 1 and 2 years post-delandistrogene moxeparvovec infusion (**Figure 2**)
- NSAA total scores appeared to plateau with increasing micro-dystrophin expression, as expected and consistent with non-clinical motor function data[10,11]
- An approximately linear relationship was maintained at Year 1, while at Year 2 a saturating profile was observed
- MRI FF across all analyzed skeletal muscle tissues showed a statistically significant correlation with all functional endpoints, with higher fat composition indicating worse functional efficacy (**Figure 3**)

Figure 2 *Week 12 delandistrogene moxeparvovec micro-dystrophin expression versus NSAA total score at 1 and 2 years post-infusion*



N: number of unique patients.
*For each patient, two replicates per muscle biopsy sample were averaged, followed by averaging the values from the two biopsy blocks.

Figure 3 *Time-matched correlation between skeletal muscle MRI FF and functional outcomes at 1 and 2 years post-infusion*



Conclusions

- In patients treated with delandistrogene moxeparvovec, a statistically significant correlation was found between Week 12 micro-dystrophin expression and 1- and 2-year functional outcomes
- A stronger correlation was observed at Year 2, demonstrating a durable treatment effect
- A saturable relationship between micro-dystrophin expression and change in NSAA total score was observed at Year 2, consistent with previously published non-clinical functional data[10,11]
- These results demonstrate a quantitative relationship between biological measures and improvements in motor function
- However, low micro-dystrophin expression did not necessarily correspond to poorer functional outcomes
  - Some patients with low expression showed changes in NSAA total score comparable to those observed in patients with high expression
- Skeletal muscle MRI FF showed statistically significant correlation with functional outcomes, with higher fat correlating with reduced improvements in functional outcomes
  - This supports the potential for skeletal muscle MRI to be used as a clinically meaningful, non-invasive biomarker for monitoring DMD disease progression and treatment responses
- Results provide clinical confirmation of the delandistrogene moxeparvovec mechanism of action and treatment effect, whereby micro-dystrophin expression correlates with functional benefit and slowing of DMD progression

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Abbreviations

4SC, time to ascend 4 steps; 10MWR, 10-metre Walk/Run; 100MWR, 100-metre Walk/Run; DMD, Duchenne muscular dystrophy; FF, fat fraction; LOESS, Locally Estimated Scatterplot Smoothing; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; TTR, Time to Rise.

References

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