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Five-Year Outcomes With Delandistrogene Moxeparvovec in Patients With Duchenne Muscular Dystrophy (DMD): A Phase 1/2a Study

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Key Findings

The 5-year outcomes from Study 101 support the long-term, manageable safety profile and demonstrate stabilization or slowing of DMD disease progression with delandistrogene moxeparvovec, with a profound divergence from natural history.

Background

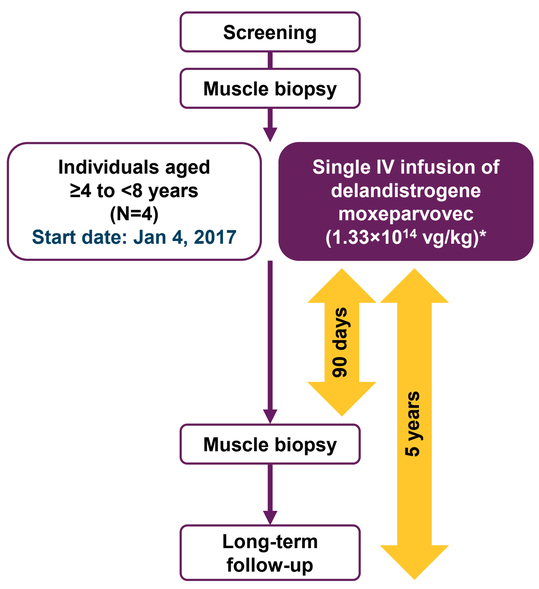
- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered, functional form of dystrophin shown to stabilize or slow disease progression in DMD[1–4]
  - It is approved in the US and in other select countries[5–12]
- Study 101 (SRP-9001-101; NCT03375164) is a Phase 1/2a, single-dose, open-label clinical trial to evaluate the safety of delandistrogene moxeparvovec in ambulatory patients with DMD (≥4 to <8 years old)[3]

Objective

- We provide a 5-year update on long-term safety and functional data from four patients treated with delandistrogene moxeparvovec
  - To contextualize functional outcomes, post hoc analyses comparing the 5-year data from Study 101 with a propensity-score-weighted EC cohort and their natural history predictions (NSAA total score) were conducted

Methods

Figure 1. *Study design: Study 101*



*All patients received one IV infusion in the peripheral limb vein at the dose 2.0×10^{14} vg/kg determined by supercoiled qPCR method (1.33×10^{14} vg/kg linear qPCR equivalent), and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene therapy delivery.

Primary outcome measure:

- Safety based on the number of patients with AEs

Key additional outcome measures:

- Change from baseline in NSAA and TFTs (including TTR from the floor and 10MWR)

Propensity-score-weighted EC cohort

- In this post hoc analysis, delandistrogene moxeparvovec-treated patients (N=4) at 5 years were compared with a propensity-score-weighted EC cohort (n=17) at 4.5 years, which included patients from the FOR-DMD study (NCT01603407)
  - FOR-DMD was an international, multicenter study comparing three corticosteroid regimens widely used for DMD[13]
- The EC cohort has 5 years of follow-up data. To match inclusion criteria for Study 101, which required ≥12 weeks of stable dose or dose equivalent of corticosteroids before baseline, the new baseline resulted in a 4.5-year follow-up time
- Propensity-score weighting incorporated baseline factors known to be prognostic of functional trajectories in DMD, namely age, NSAA total score, TTR from the floor and 10MWR, to ensure baseline comparability on these factors between the delandistrogene moxeparvovec and EC groups, as described previously[14]

Predictive controls

- Expected NSAA total score trajectories without delandistrogene moxeparvovec treatment were predicted for patients with matched baseline prognostic factors (including age and motor function) as those treated in Study 101 using a previously developed model (cTAP)

Results

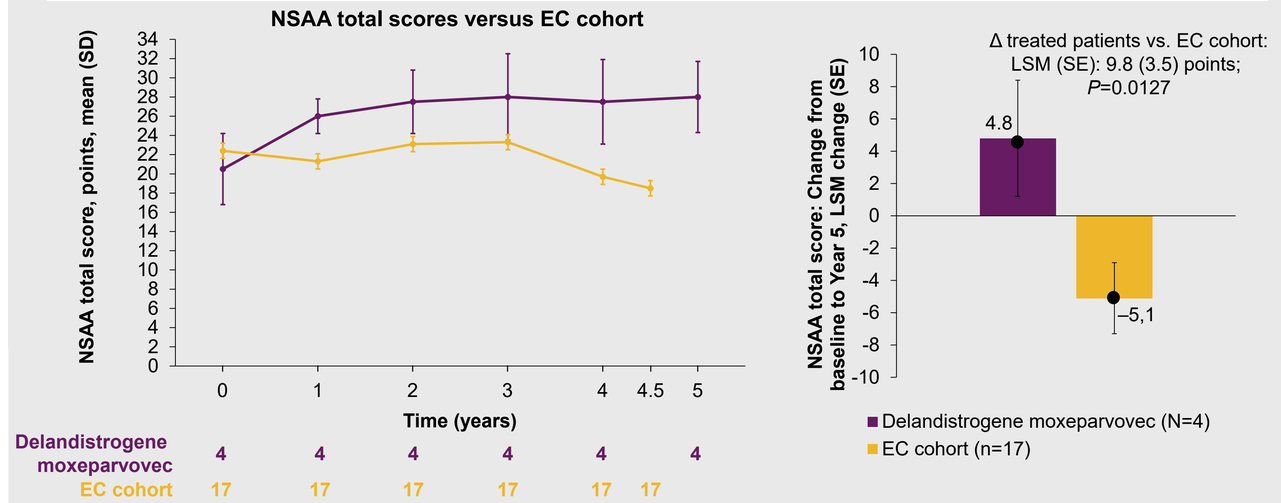
Demographics and baseline patient characteristics

- Demographics and baseline characteristics of the patients have been published previously[3]
  - EC cohort baseline characteristics were comparable to those of patients in the delandistrogene moxeparvovec group[14]
- At 5 years post-infusion, the mean (range) age of patients was 10.20 (9.07–11.12) years

Primary endpoint: Safety

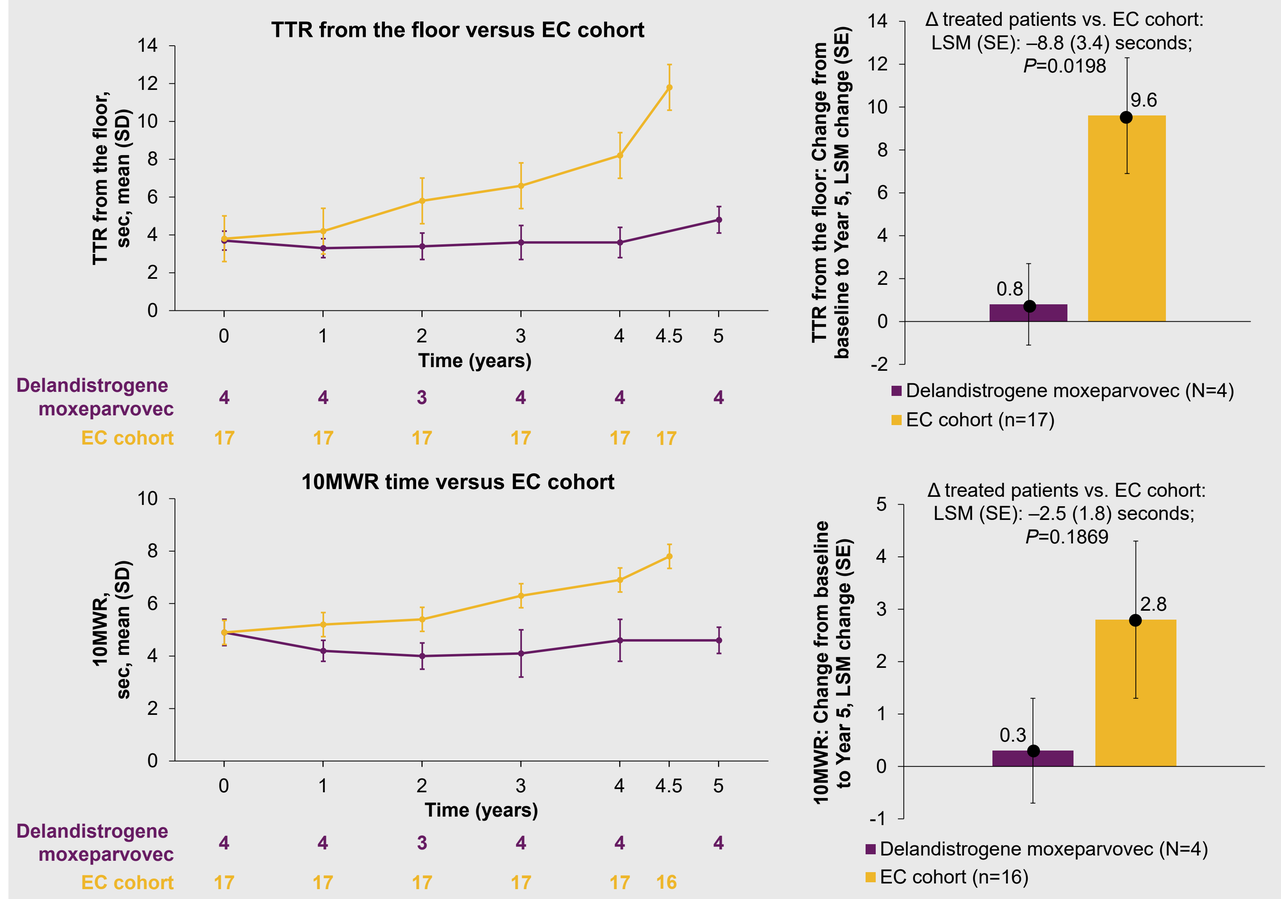
- AEs occurring at Years 1 and 4 post-treatment have been reported[3,14]
- Overall, 75 AEs were reported (most occurred ≤70 days post-infusion)
- Eighteen TR-TEAEs were reported (all mild or moderate)
  - The most common were vomiting and increased liver enzymes (all resolved)
- There were no SAEs, clinically significant complement-mediated AEs, study discontinuations or deaths

Figure 2. *Change from baseline to Year 5 in NSAA total score in the delandistrogene moxeparvovec group versus EC cohort*



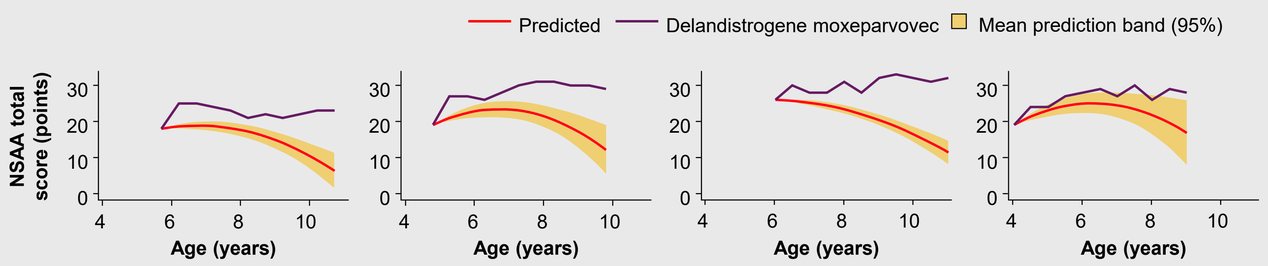
- Delandistrogene moxeparvovec-treated patients showed a sustained increase in NSAA total score over 5 years, with a statistically significant and clinically meaningful difference at Year 5 compared with the EC cohort (Figure 2)
- All delandistrogene moxeparvovec-treated patients remained ambulant throughout the study duration whilst four patients in the EC cohort experienced loss of ambulation at 8.4–11.6 years old (between 18 and 54 months post-adjusted baseline)

Figure 3. *Change from baseline to Year 5 in TTR from the floor (sec) and 10MWR (sec) in the delandistrogene moxeparvovec group versus EC cohort*



- There was a statistically significant and clinically meaningful difference in TTR from the floor in the delandistrogene moxeparvovec-treated patients versus the EC cohort at Year 5 (Figure 3, top panel)
- 10MWR time was maintained amongst delandistrogene moxeparvovec-treated patients over 5 years, demonstrating a clinically meaningful difference versus the EC cohort at Year 5 (Figure 3, bottom panel)

Figure 4. *NSAA total score of individual delandistrogene moxeparvovec-treated patients versus their natural history predictions (cTAP model)*



- cTAP modeling showed an increase in divergence of NSAA total score trajectory of delandistrogene moxeparvovec-treated patients versus their natural history predictions over 5 years of follow-up (Figure 4)

Conclusions

- Over the 5-year follow-up period, there were no new safety signals reported after the initial 70 days post-infusion, supporting the manageable and consistent safety profile of delandistrogene moxeparvovec
- Long-term outcomes from this study support the biological role of functional dystrophin and indicate that delandistrogene moxeparvovec stabilizes or slows DMD disease progression with an increase in divergence from natural history over time
- There was a statistically significant and clinically meaningful difference in NSAA and TTR from the floor in the delandistrogene moxeparvovec-treated patients versus the EC cohort at Year 5
- 10MWR time was maintained amongst delandistrogene moxeparvovec-treated patients over 5 years, demonstrating a clinically meaningful difference versus the EC cohort at Year 5
- The NSAA findings were further corroborated using an independent model-based approach (cTAP) that supported the increase in divergence in disease progression from natural history over time with treatment

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ABBREVIATIONS

10MWR, 10-Metre Walk/Run; AE, adverse event; cTAP, collaborative Trajectory Analysis Project; DMD, Duchenne muscular dystrophy; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; IV, intravenous; LSM, least squares mean; NSAA, North Star Ambulatory Assessment; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; SE, standard error; TFT, timed function test; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise; vg, vector genome.

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