PROMIS Parent Proxy Mobility Scores in Patients Treated With Delandistrogene Moxeparvovec in EMBARK Part 2 Compared With External Controls

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Background

- Duchenne muscular dystrophy (DMD) is an X-linked, degenerative neuromuscular disease caused by pathogenic variants in the *DMD* gene leading to progressive muscle weakness and eventually loss of ambulatory function[1,2]
- Delandistrogene moxeparvovec, a gene transfer therapy that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, is approved in the US for the treatment of DMD[3]
- Patient- and caregiver-reported outcomes can help evaluate a treatment's ability to slow functional decline by providing meaningful insight into progression of DMD
  - Patient-Reported Outcomes Measurement Information System (PROMIS) is a group of person-centered items developed and validated to assess health-related quality of life that includes the PROMIS Parent Proxy Mobility (PROMIS Mobility) item bank, which enables parents to assess their children's movement[4,5]

Objective

- To evaluate the effect of delandistrogene moxeparvovec treatment on PROMIS Mobility scores in patients with DMD by comparing patients treated in Part 2 of the EMBARK study with external controls (ECs)

Methods

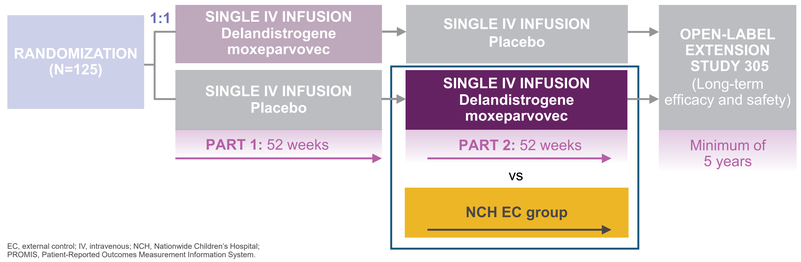
Data sources

- This exploratory analysis used data from 2 sources (**Figure 1**):
  - Data from patients who received delandistrogene moxeparvovec in EMBARK Part 2 composed the treatment group
    - EMBARK was a 2-part phase 3 crossover study aimed to assess the efficacy and safety of delandistrogene moxeparvovec (single intravenous administration of 1.33×10^{14} vector genomes per kilogram) in ambulatory patients with DMD 4 to 7 years of age at study enrollment[6]
    - In Part 2, patients who received placebo in Part 1 received delandistrogene moxeparvovec, whereas those treated with delandistrogene moxeparvovec in Part 1 received placebo
  - Data from patients with DMD receiving routine treatment at the Nationwide Children's Hospital (NCH) were used to form the EC group, given that there was no concurrent, delandistrogene moxeparvovec-naïve control arm for patients who received the gene therapy in Part 2 of the EMBARK study

Inclusion criteria

- Delandistrogene moxeparvovec-treated group: Male patients aged 5 to 9 years who initiated treatment with delandistrogene moxeparvovec at the start of Part 2 of the EMBARK study
- EC group: Male patients aged 5 to 9 years who were treated at the NCH, and were ambulatory (or <30 s at 10-minute walk-run test) at baseline and had ≥1 postbaseline observation

Figure 1 *EMBARK Study Design and Part 2 PROMIS Mobility Analysis With EC*



EC, external control; IV, intravenous; NCH, Nationwide Children's Hospital; PROMIS, Patient-Reported Outcomes Measurement Information System.

Inverse probability of treatment weighting

- Inverse probability of treatment weighting (IPTW) using average treatment effect on the treated weights was applied to correct for nonrandomized treatment assignment by weighting the EC population to achieve balance with the treated population on confounders at baseline
  - Key confounders at baseline were age, PROMIS Mobility mean raw score, and North Star Ambulatory Assessment (NSAA) score

Primary analysis

- The primary analysis compared the rate of change in PROMIS Mobility scores for the EMBARK Part 2 cohort versus the EC cohort using a linear mixed-effects model that included fixed effects for age, treatment, age-by-treatment interaction, as well as baseline values for age, PROMIS Mobility score, and NSAA score; the model also included a patient-level random intercept

Exploratory analysis

- An exploratory analysis assessed the effect of treatment with delandistrogene moxeparvovec on time to meaningful improvement in PROMIS Mobility
  - The threshold for meaningful improvement in PROMIS Mobility was derived from an analysis using EMBARK Part 1 data linking Caregiver Global Impression of Severity (CaGI-S) of impairment in physical abilities to PROMIS Mobility scores
  - Estimation of within-patient thresholds of meaningful change were calculated using anchor-based methods to establish a responder threshold
  - The proportion of patients experiencing meaningful improvement events was summarized for both groups
  - The treatment effect on time to meaningful improvement (defined as the first time at which the change from baseline is equivalent or greater than the improvement threshold and is sustained until the end of follow-up) was assessed using IPTW-weighted Kaplan-Meier analysis, which estimated the difference in proportion of patients with improvement at 1 year

Results

Study population

- All 60 patients treated with delandistrogene moxeparvovec in Part 2 of EMBARK were included in the analysis
- A total of 25 patients in the NCH data set met the inclusion criteria for comparison with the EMBARK Part 2 cohort and made up the EC group
- After IPTW, key covariates had a standardized mean difference of <0.2 across groups (**Table 1**)

Table 1 *Baseline Characteristics of Analysis Population*

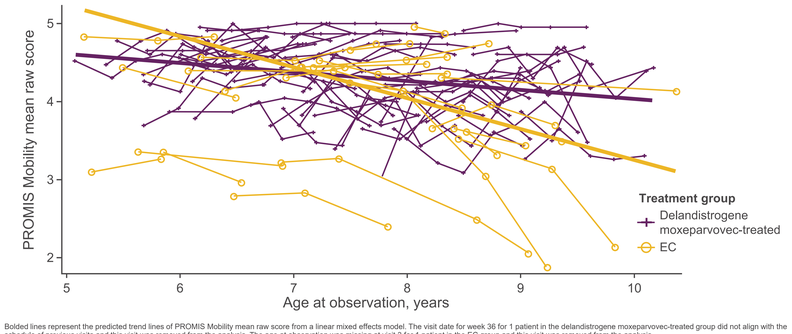
Mean (SD)	Delandistrogene moxeparvovec-treated group (N=60)	EC group (N=25)	SMD	
			Pre-weighting	Post-weighting[a]
Age, y	7.18 (1.06)	6.97 (1.15)	0.19	−0.01
PROMIS Mobility raw score	4.23 (0.45)	4.07 (0.61)	0.31	−0.01
Functional measures				
NSAA score	24.8 (4.8)	20.6 (5.9)	0.78	0.18
10MWR time, s	5.01 (1.26)	5.84 (1.86)	−0.52	−0.05
10MWR velocity, m/s	2.09 (0.42)	1.85 (0.47)	0.55	0.09

[a]The EC population was weighted by propensity score.
10MWR, 10-meter walk/run; EC, external control; NSAA, North Star Ambulatory Assessment; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SMD, standardized mean difference.

Difference in rate of change in PROMIS Mobility scores

- Patients treated with delandistrogene moxeparvovec had a nominally significant slower PROMIS Mobility rate of decline compared with patients in the EC group (difference in linear mixed-effects model slope, 0.281; 95% CI, 0.041-0.520; *P*=0.022; **Figure 2**)

Figure 2 *PROMIS Mobility Score Observed in Patients Treated With Delandistrogene Moxeparvovec Versus Patients in the EC Group Alongside Predicted Trend Lines*



Bolded lines represent the predicted trend lines of PROMIS Mobility mean raw score from a linear mixed effects model. The visit date for week 36 for 1 patient in the delandistrogene moxeparvovec-treated group did not align with the schedule of previous visits and this visit was removed from the analysis. The age at observation was missing at visit 3 for 1 patient in the EC group and this visit was removed from the analysis.
EC, external control; PROMIS, Patient-Reported Outcomes Measurement Information System.

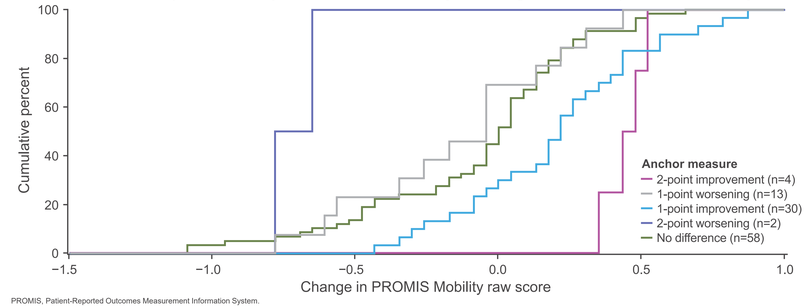
Estimation of a meaningful change threshold

- An anchor-based analysis of PROMIS Mobility EMBARK Part 1 data yielded an estimated PROMIS Mobility improvement threshold of 0.2 (**Figure 3**)
  - The Pearson correlation between change from baseline to week 52 in PROMIS Mobility score and the CaGI-S parameter, "How would you rate the severity of impairment in the child's physical ability at this time?," was −0.435

Limitations

- Because these were exploratory analyses and were not pre-specified, *P* values were not adjusted for multiplicity and should therefore be interpreted as nominally significant
- This analysis was limited by the inability to adjust for steroid use or to match patients across all baseline characteristics, such as comorbidities
- The comparator arm used for this analysis was from an external cohort, which had a relatively small sample size

Figure 3 *Empirical Cumulative Distribution Function of Change From Baseline to Week 52 in PROMIS Mobility Score and Impairment in Physical Abilities as Rated by the Caregiver Global Impression of Severity Scale*

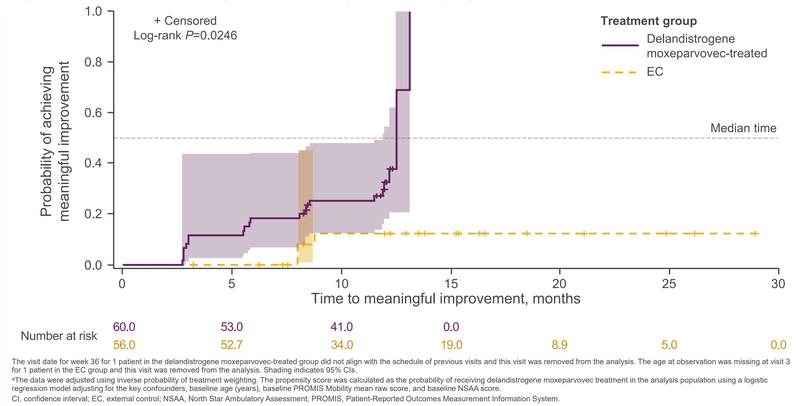


PROMIS, Patient-Reported Outcomes Measurement Information System.

Meaningful improvement in PROMIS Mobility scores

- In total, 48% (29/60) of patients treated with delandistrogene moxeparvovec and 12% (3/25) of patients in the EC group experienced improvement events in PROMIS Mobility
- The onset for improvement events occurred earlier in patients treated with delandistrogene moxeparvovec and continued to accumulate over time (**Figure 4**)
  - The difference in proportion of meaningful improvement at 1 year was higher for patients treated with delandistrogene moxeparvovec (log-rank *P*=0.0246)

Figure 4 *Time to First Meaningful Improvement (Adjusted Analysis)[a]*



The visit date for week 36 for 1 patient in the delandistrogene moxeparvovec-treated group did not align with the schedule of previous visits and this visit was removed from the analysis. The age at observation was missing at visit 3 for 1 patient in the EC group and this visit was removed from the analysis. Shading indicates 95% CIs.
[a]The data were adjusted using inverse probability of treatment weighting. The propensity score was calculated as the probability of receiving delandistrogene moxeparvovec treatment in the analysis population using a logistic regression model adjusting for the key confounders, baseline age (years), baseline PROMIS Mobility mean raw score, and baseline NSAA score.
CI, confidence interval; EC, external control; NSAA, North Star Ambulatory Assessment; PROMIS, Patient-Reported Outcomes Measurement Information System.

Conclusions

- The results of this study are consistent with earlier findings of delandistrogene moxeparvovec,[6-8] demonstrating its potential to alter the trajectory of DMD by slowing disease progression
  - Slower disease progression was observed in patients treated with delandistrogene moxeparvovec in this analysis of the EMBARK study data, as demonstrated by a slower decline in PROMIS Mobility scores compared with an EC group
  - Patients in the treatment group were also more likely to achieve a clinically meaningful improvement in PROMIS Mobility, which occurred earlier than for patients in the EC group

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