Safety and Efficacy of Delandistrogene Moxeparvovec Versus Placebo in Duchenne Muscular Dystrophy: Phase 3 EMBARK Primary Results

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What does this study mean for the DMD community

- **The totality of findings from all functional outcomes assessed in the EMBARK study, including the timed functional tests, supports modification of disease trajectory with delandistrogene moxeparvovec with a manageable safety profile.**
  - EMBARK Part 2 will provide 2-year data for patients treated in Part 1, allowing progression to be monitored and adding to longer-term data.

Conclusions

- At Week 52, the safety profile of delandistrogene moxeparvovec was consistent with prior experience, and AEs were medically manageable with appropriate monitoring and treatment, with no new safety signals identified, and no deaths, study discontinuations or clinically relevant complement-mediated AEs.
- Although delandistrogene moxeparvovec did not show a statistically significant difference in the primary endpoint at Week 52 versus placebo, there was a clear separation between treatment groups, most evident on key secondary and other functional endpoints that consisted of well-validated measures of ambulatory function in DMD.
- The GST supported the totality of evidence of the beneficial effect of delandistrogene moxeparvovec on motor function and strongly indicated the presence of a functional treatment effect.
- A post hoc analysis of TTR showed a marked difference in the proportion of delandistrogene moxeparvovec-treated patients progressing to a TTR >5 seconds, a prognostic marker for accelerated disease progression and earlier loss of ambulation.

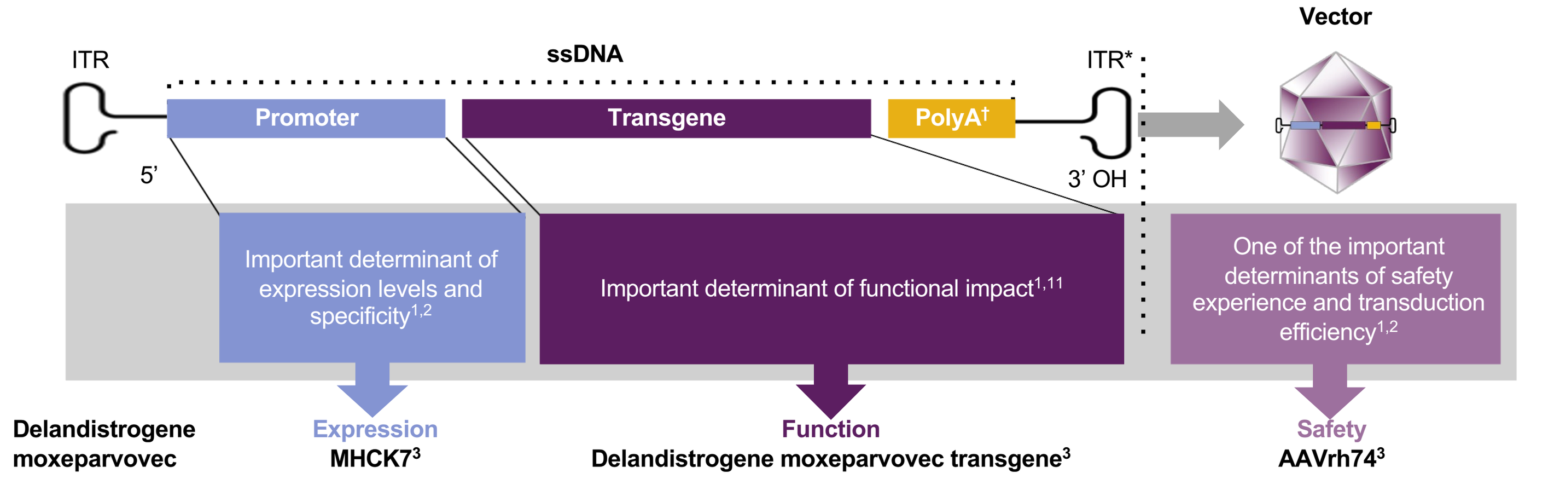
Objective

- We present an overview of the 1-year safety and functional outcomes from Part 1 of EMBARK.

Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered protein that retains key functional domains of the wild-type protein.[1–3]
- As of April 2024, delandistrogene moxeparvovec is approved in the USA, UAE, Qatar, Kuwait, Bahrain and Oman for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene. Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.[4–9]
- EMBARK (NCT05096221)[10] is a Phase 3, two-part, multinational, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of delandistrogene moxeparvovec in patients with DMD aged ≥4 to <8 years.

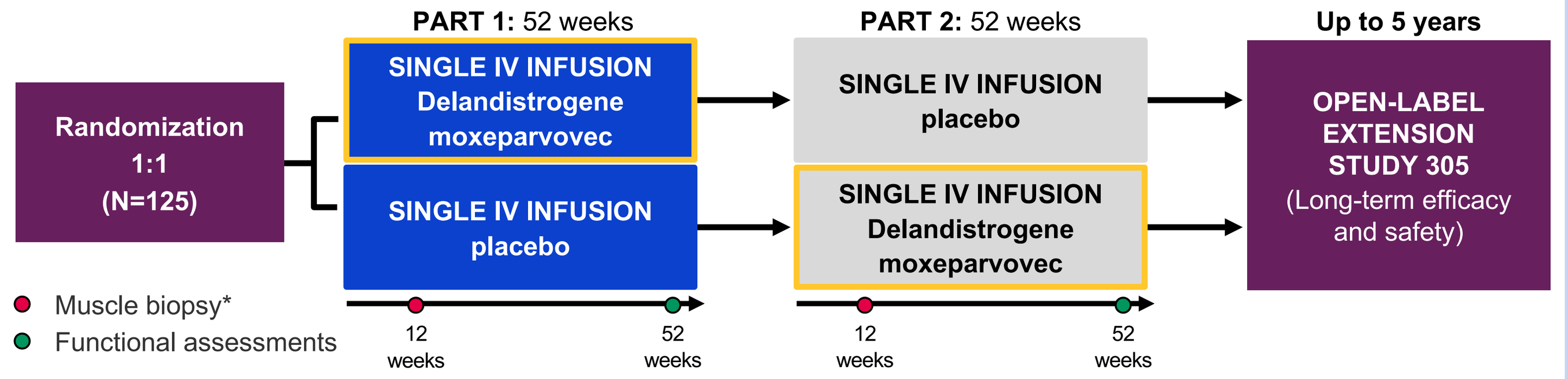
Figure 1. Overview of delandistrogene moxeparvovec



*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.

Study design and endpoints[10]

Figure 2. EMBARK study design schematic



- Stratification based on age at randomization (≥4 to <6 or ≥6 to <8 years) and NSAA score at screening (≤22 vs. >22).

*Only a subset of patients will receive a muscle biopsy for expression assessments, based on site experience and feasibility.

Key inclusion criteria

- Ambulatory males aged ≥4 to <8 years at randomization.
- Confirmed DMD diagnosis (*DMD* mutation fully contained between exons 18 to 79 [inclusive]).
- Ability to cooperate with motor assessment testing.
- NSAA 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 titers <1:400 (i.e. not elevated).

Study design and endpoints[10] (cont.)

Endpoints

Primary endpoint
- Change from baseline to Week 52 in NSAA total score.

Key secondary functional endpoints
- Change from baseline to Week 52 in:
  - TTR
  - 10MWR.

Other secondary functional endpoints
- Change from baseline to Week 52 in:
  - SV95C as measured by a wearable device (Syde®)
  - 100MWR
  - Time to ascend 4 steps.

Safety endpoints
- TEAEs, SAEs and AEs of special interest.
- Clinically significant changes in laboratory assessments.

Additional pre-specified efficacy analyses
- GST for totality of evidence analysis on a composite of endpoints through permutations.[12,13]

The primary endpoint and secondary endpoints were tested using a statistical hierarchy to control the overall Type I error at a 2-sided level of 0.05*

*Additional endpoints were included in the sequential testing, that are not reported in this presentation.

Results

Demographics and clinical characteristics

- Patient demographics and baseline clinical characteristics were balanced between delandistrogene moxeparvovec and placebo groups.

Characteristic	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)	All (N=125)
Mean age, years (SD)	5.98 (1.06)	6.08 (1.05)	6.03 (1.05)
4–5 years, n (%)	30 (47.6)	29 (46.8)	59 (47.2)
6–7 years, n (%)	33 (52.4)	33 (53.2)	66 (52.8)
Mean dosing weight, kg (SD)	21.29 (4.62)	22.37 (6.42)	21.83 (5.59)
Mean time since corticosteroid treatment started, years (SD)	1.07 (0.92)	0.97 (0.83)	1.02 (0.88)
Baseline functional assessments			
Mean NSAA total score, points (SD)	23.10 (3.75)	22.82 (3.78)	22.96 (3.75)
Mean TTR, seconds (SD)	3.52 (0.81)	3.60 (0.68)	3.56 (0.75)
Mean 10MWR, seconds (SD)	4.82 (0.79)	4.92 (0.73)	4.87 (0.76)
Mean SV95C, meters/second (SD)*	1.82 (0.30)	1.77 (0.29)	1.79 (0.30)
Mean 100MWR, seconds (SD)†	60.67 (15.55)	63.01 (17.01)	61.80 (16.25)
Mean time to ascend 4 steps, seconds (SD)‡	3.17 (1.01)	3.37 (1.09)	3.27 (1.05)

*SV95C: Delandistrogene moxeparvovec n=61, placebo n=62, total N=123. †100MWR: Delandistrogene moxeparvovec n=63, placebo n=59, total N=122. ‡Time to ascend 4 steps: Delandistrogene moxeparvovec n=63, placebo n=61, total N=124.

Safety overview

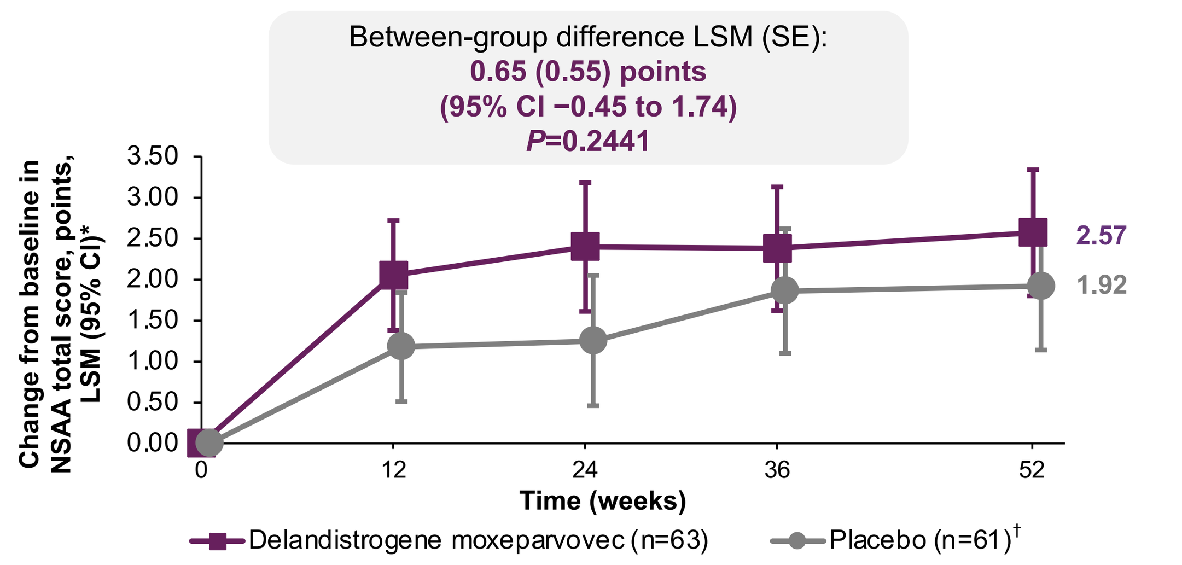
	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)
Patients with any TEAE, n (%)	62 (98.4)	57 (91.9)
TEAEs, n	664	502
Patients with any TR-TEAE, n (%)	48 (76.2)	17 (27.4)
TR-TEAEs, n	235	43
Patients with any TR-SAE, n (%)	7 (11.1)	0
TR-SAEs, n	10	0
Patients with an AE leading to study discontinuation, n (%)	0	0
Deaths, n (%)	0	0

- The safety profile of delandistrogene moxeparvovec in EMBARK was **consistent with experience from early phase studies**.
- AEs were **medically manageable** with appropriate monitoring and treatment.
- There were **no clinically relevant complement activation AEs, no deaths and no study discontinuations**.

Results (cont.)

Primary endpoint

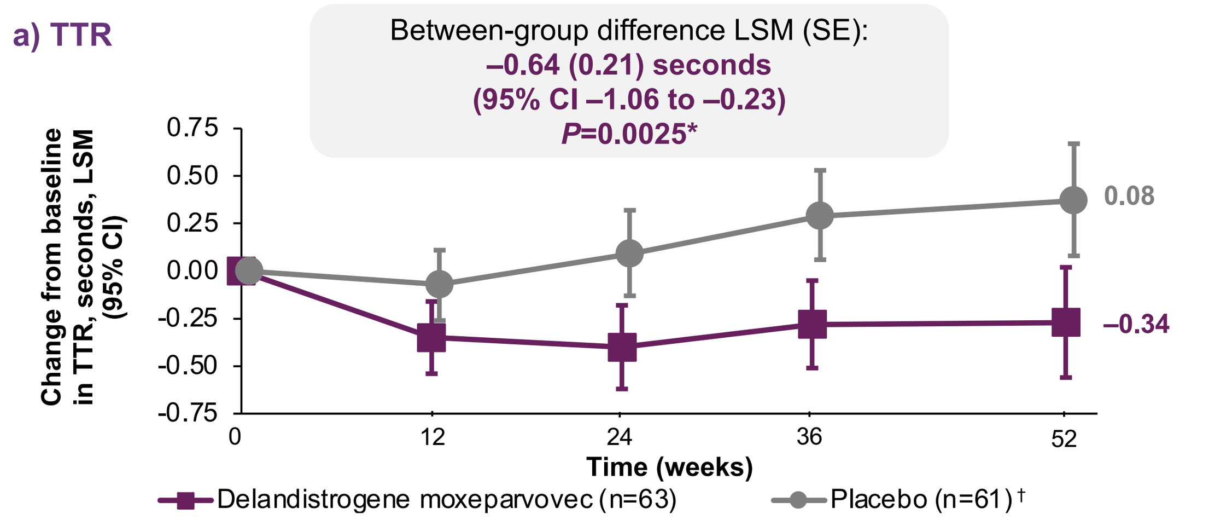
Figure 3. Change from baseline to Week 52 in NSAA total score

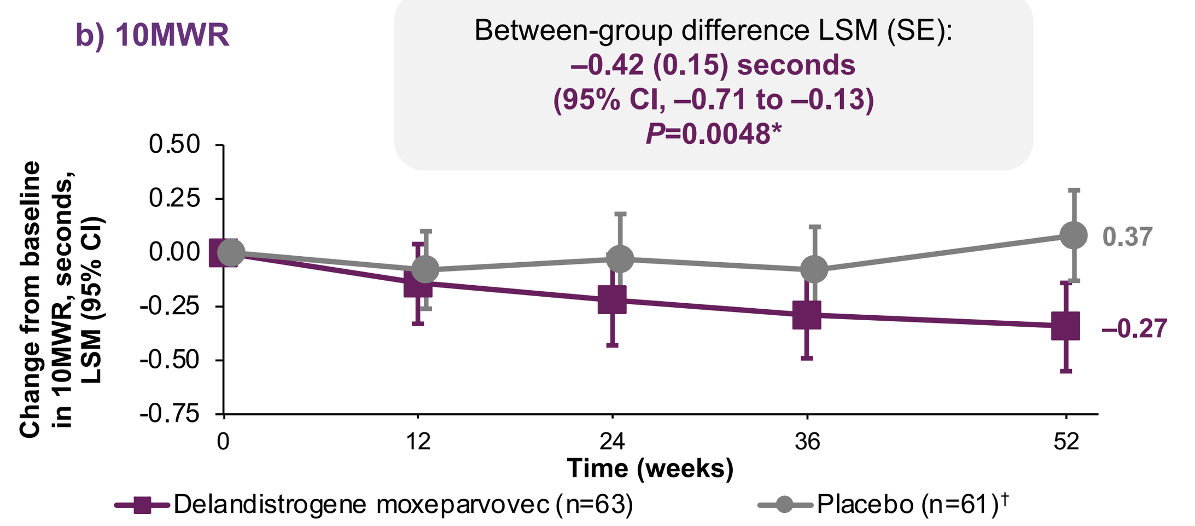


*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †One patient in the placebo group had missing data at Week 52; the patient's functional tests were marked as invalid by the clinical evaluator due to back pain from compression fractures.

Key secondary functional endpoints

Figure 5. Change from baseline to Week 52 in a) TTR and b) 10MWR





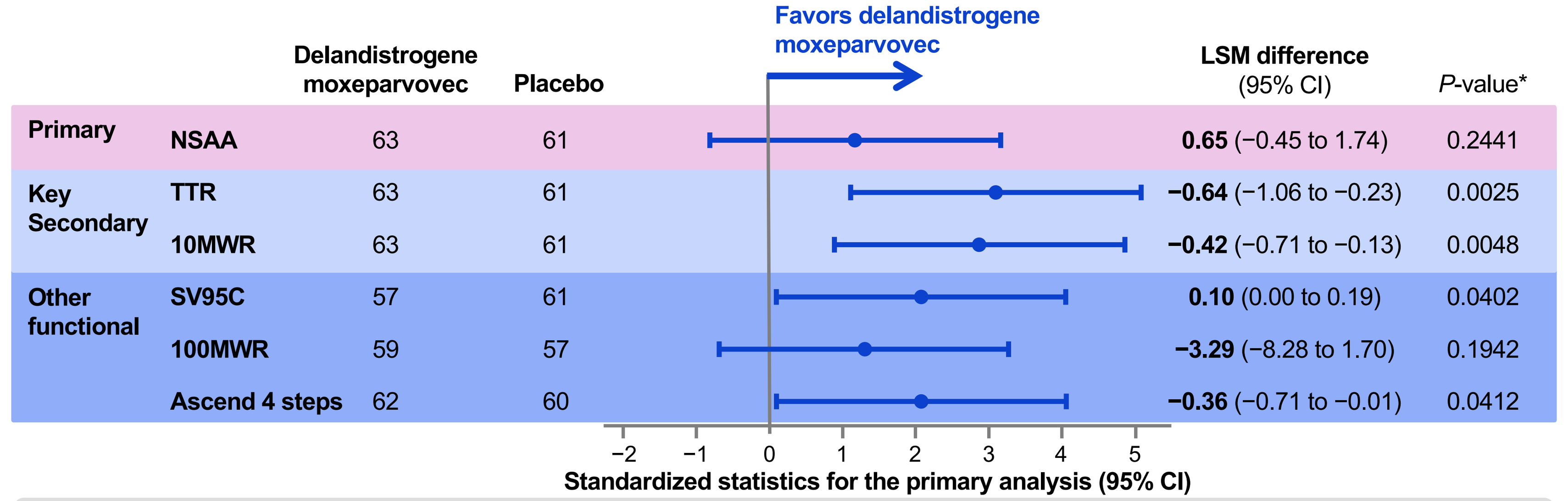
- Negative values indicate an improvement in the time taken to achieve these endpoints.
- The separation between groups was **clinically relevant for both TTR and 10MWR.**

*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing of endpoints are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †One patient in the placebo group had missing data at Week 52; the patient's functional tests were marked as invalid by the clinical evaluator due to back pain from compression fractures.

- Other secondary functional endpoints are shown in Supplementary Figures 1–3.

Summary of functional endpoints

Figure 4. Functional endpoints at Week 52 in the overall population



*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects

LSMs (of change from baseline) and CIs were standardized by dividing by the SE. Negative values for timed function tests (TTR, 10MWR, 100MWR and time to ascend 4 steps) show an improvement in the time taken to achieve these endpoints. LSM differences are on original scale (without SE adjustment). Signs of timed function tests were reversed in the forest plot to align favorable directions among endpoints. Numerical results of LSM difference kept the original signs.

Pre-specified GST

- A pre-specified **GST** was performed as an additional exploratory analysis to assess overall treatment effects.
- The test was on a composite of functional endpoints (Primary endpoint: NSAA total score; Key secondary functional endpoints: TTR, 10MWR; Other secondary functional endpoints: SV95C, 100MWR, ascend 4 steps).
- The GST **supported the totality of evidence of treatment benefit with delandistrogene moxeparvovec** compared with placebo (***P*=0.0044**).

Post hoc analyses on TTR

- All patients had a TTR <5 seconds at screening.
- With delandistrogene moxeparvovec treatment, **fewer patients progressed to a TTR >5 seconds** compared with placebo.
- A TTR >5 seconds is a threshold of **prognostic significance for loss of ambulation.**[14,15]

Patients with TTR >5 seconds at Week 52		Reduction in odds
Delandistrogene moxeparvovec (n=63)	Placebo (n=61)	
3%	16%	91% (*P*=0.0135)

NSAA
- The heterogeneity of DMD disease progression is a challenge when designing trials of short duration in this study population and age range (4–7-year-olds).[16,17]
  - Motor function may still be improving, maintaining or starting to decline.
- A 1-point difference in the NSAA indicates different ranges of function, from inability to do a task, to using compensation, or performing with no compensation.[16] In younger patients, neurodevelopmental maturation might also affect these achievements.[18]

TFTs
- TFTs such as TTR and 10MWR may be more sensitive measures of functional change in this age range and study duration.[16]

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Abbreviations

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; CI, confidence interval; DMD, Duchenne muscular dystrophy; GST, global statistical test; ITR, inverted terminal repeat; IV, intravenous; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; OH, hydroxide; polyA, polyadenylation; rAAV, recombinant adeno-associated virus; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; SV95C, stride velocity 95th centile; TEAE, treatment-emergent adverse event; TEAE, treatment-emergent adverse event; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise; UAE, United Arab Emirates.

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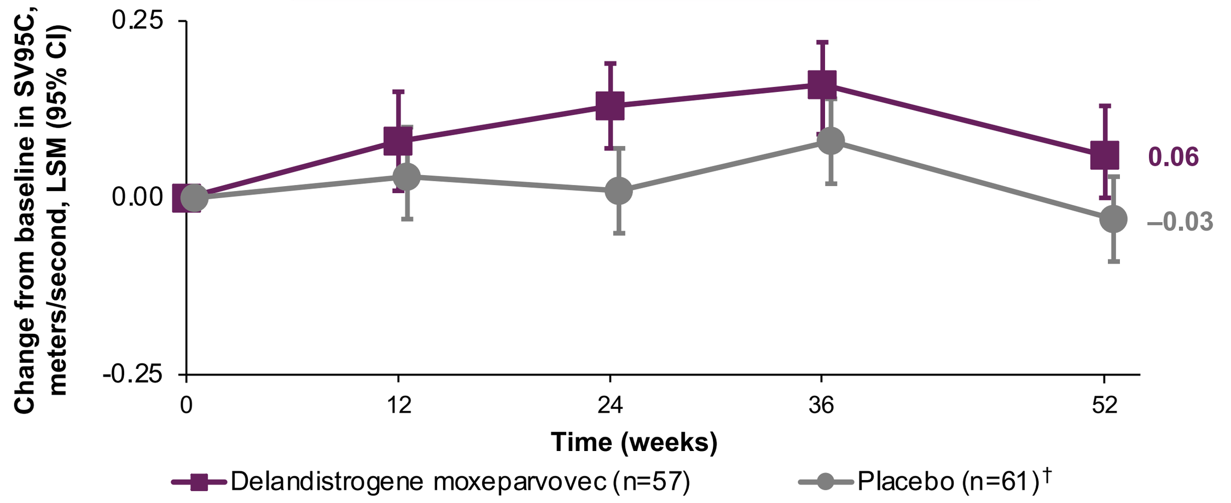
*At the time of study; †Presenting on behalf of the author group (email address: medinfo@sarepta.com).

Supplementary information

Other secondary functional endpoint:
Supplementary Figure 1. Change from baseline to Week 52 in SV95C

Between-group difference LSM (SE):
0.10 (0.05) meters/second (95% CI 0.00 to 0.19)
P=0.0402*



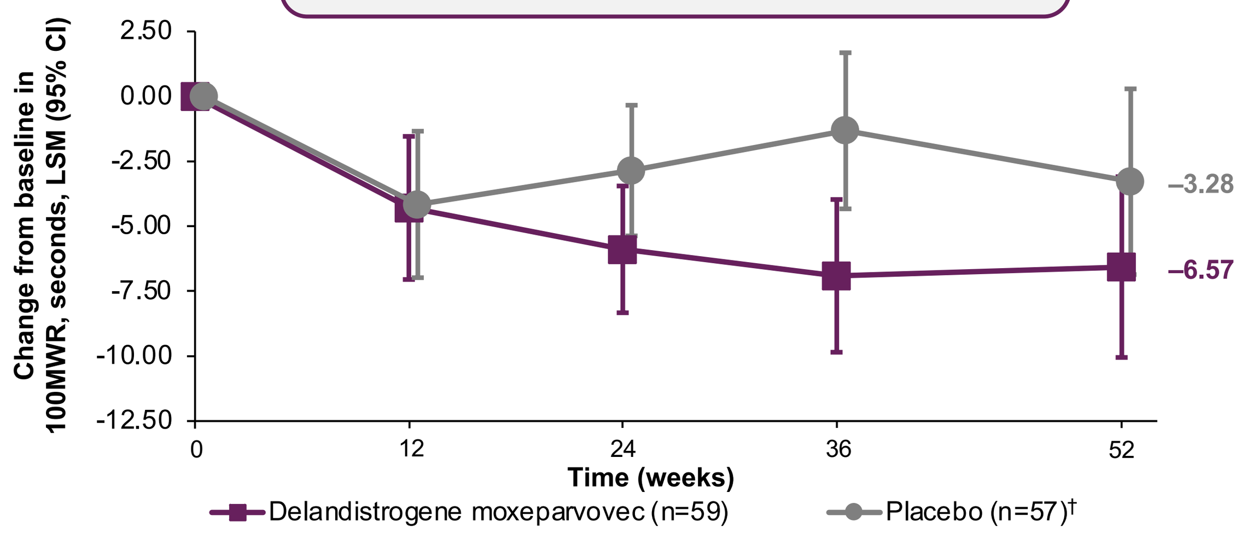
- SV95C is a **digital objective endpoint** of ambulatory performance in patients' **normal daily environment**
- Patients in EMBARK **wore the device on each ankle for 3 weeks** prior to the clinic visits

- The change from baseline **met the published MCID** by the EMA[1]
- EMBARK is the first randomized, placebo-controlled trial in DMD that **showed clinical relevance to a therapy based on SV95C** from a wearable device

*Since the primary endpoint did not meet statistical significance, all P-values resulting from subsequent hierarchical testing of endpoints are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †A small number of patients did not have sufficient recorded hours at Week 52 for analysis.

Other secondary functional endpoint:
Supplementary Figure 2. Change from baseline to Week 52 in 100MWR

Between-group difference LSM (SE):
–3.29 (2.52) seconds (95% CI –8.28 to 1.70)
P=0.1942*



- Negative values indicate an improvement in the time taken to achieve this endpoint

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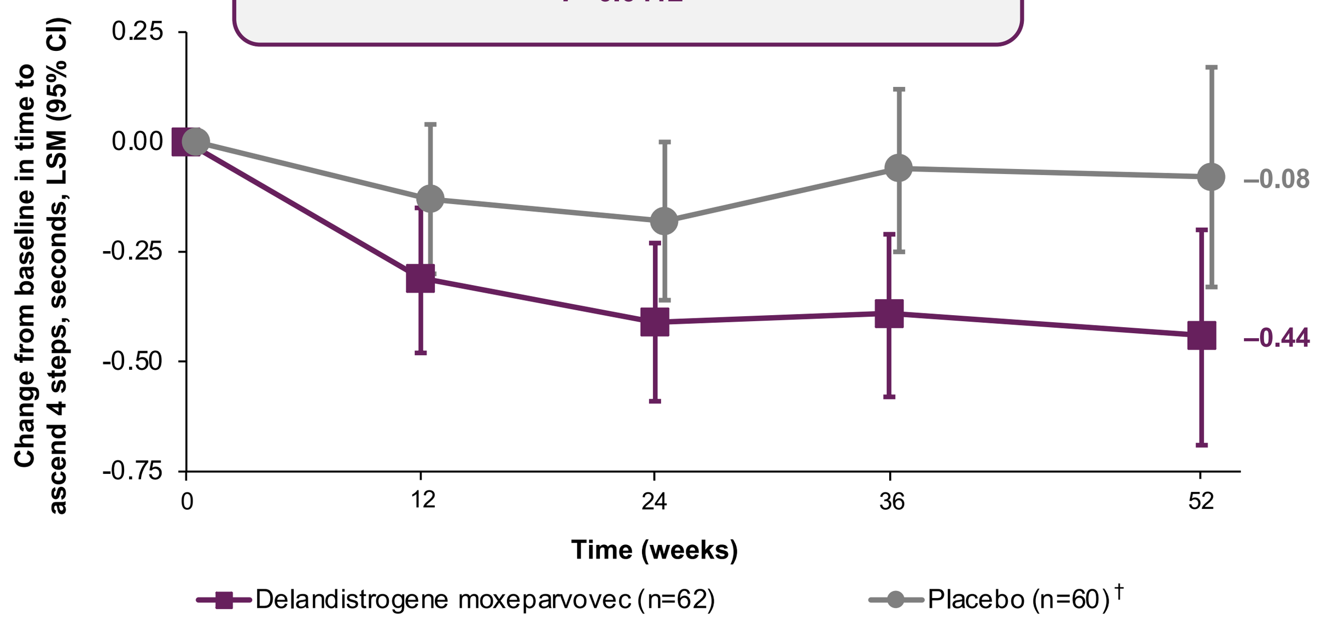
Other secondary functional endpoint:
Supplementary Figure 3. Change from baseline to Week 52 in time to ascend 4 steps

Between-group difference LSM (SE):
–0.36 (0.18) seconds (95% CI –0.71 to –0.01)
P=0.0412*



- Negative values indicate an improvement in the time taken to achieve this endpoint

- The separation between groups was **clinically relevant**

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Abbreviations

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; CI, confidence interval; DMD, Duchenne muscular dystrophy; GST, global statistical test; ITR, inverted terminal repeat; IV, intravenous; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; OH, hydroxide; polyA, polyadenylation; rAAV, recombinant adeno-associated virus; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; SV95C, stride velocity 95th centile; TEAE, treatment-emergent adverse event; TEAE, treatment-emergent adverse event; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise; UAE, United Arab Emirates.

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