Safety and efficacy of delandistrogene moxeparvovec versus placebo in Duchenne muscular dystrophy: Phase 3 EMBARK primary results

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[†]At the time of Part 1 of EMBARK (currently employed by Sarepta Therapeutics, Inc.). *Presenting on behalf of the author group (email address: medinfo@sarepta.com).

What does this study mean for the DMD community?

- In Part 1 (52 weeks) of the EMBARK study, key secondary and other functional endpoints, consisting of well-validated measures of ambulatory function in DMD, numerically favoured delandistrogene moxeparvovec.
  - These results are consistent with long-term results from earlier delandistrogene moxeparvovec trials and the essential myoprotective role of functional dystrophin.

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 significant complement-mediated AEs.
- Although delandistrogene moxeparvovec did not show a statistically significant difference in the primary endpoint of change from baseline to Week 52 in NSAA total score 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 treatment effect with delandistrogene moxeparvovec and indicated the presence of a functional treatment effect.
- A post hoc analysis of TTR showed a greater proportion of patients in the placebo group progressing to a TTR >5 seconds, a prognostic marker for accelerated disease progression and earlier loss of ambulation, demonstrating the potential for delandistrogene moxeparvovec to modify the course of the disease.

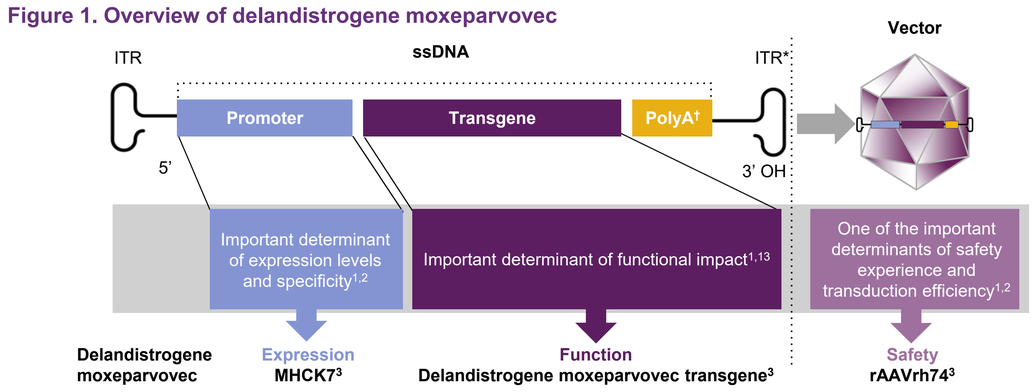
OBJECTIVE

- We present an overview of the 1-year safety and functional outcomes from Part 1 of the Phase 3 EMBARK study.

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 stabilise or slow disease progression in DMD (**Figure 1**);[1–4] it is approved in the US and in other select countries.[5–11]
- EMBARK (NCT05096221)[12] is a Phase 3, two-part, multinational, randomised, double-blind, placebo-controlled study assessing the safety and efficacy of delandistrogene moxeparvovec in patients with DMD aged ≥4 to <8 years (**Figure 2**).

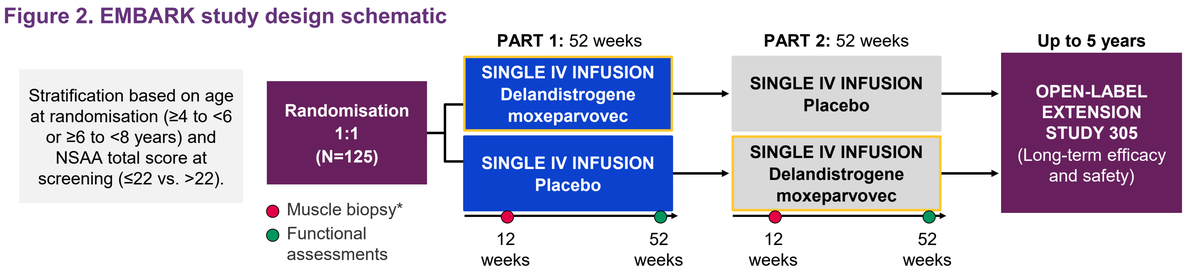
Figure 1. Overview of delandistrogene moxeparvovec



*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[12]

Figure 2. EMBARK study design schematic



*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 randomisation
- Confirmed DMD diagnosis (*DMD* mutation fully contained within exons 18–79 [inclusive])
- Ability to cooperate with motor assessment testing
- NSAA total score >16 and <29 points at screening
- TTR <5 seconds at screening
- Receiving a stable daily dose of oral corticosteroids for ≥12 weeks before screening
- rAAVrh74 total binding antibody titres <1:400 (i.e. not elevated).

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.[14,15]

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 poster.

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)
Age, mean (SD), years	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)
Dosing weight, mean (SD), kg	21.29 (4.62)	22.37 (6.42)	21.83 (5.59)
Time since corticosteroid treatment started, mean (SD), years	1.07 (0.92)	0.97 (0.83)	1.02 (0.88)
Baseline functional assessments			
NSAA total score, mean (SD), points	23.10 (3.75)	22.82 (3.78)	22.96 (3.75)
TTR, mean (SD), seconds	3.52 (0.81)	3.60 (0.68)	3.56 (0.75)
10MWR, mean (SD), seconds	4.82 (0.79)	4.92 (0.73)	4.87 (0.76)
SV95C, mean (SD), metres/second*	1.82 (0.30)	1.77 (0.29)	1.79 (0.30)
100MWR, mean (SD), seconds†	60.67 (15.55)	63.01 (17.01)	61.80 (16.25)
Time to ascend 4 steps, mean (SD), seconds‡	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 significant complement activation AEs, no deaths and no study discontinuations**.

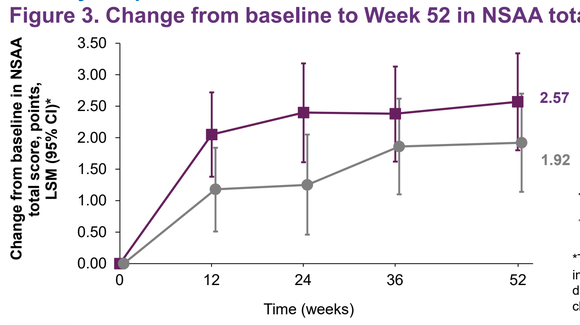
TR-TEAEs occurring in >10% of patients, n (%)	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)
Vomiting	34 (54.0)	0
Nausea	20 (31.7)	5 (8.1)
Decreased appetite	17 (27.0)	1 (1.6)
GLDH increased*	15 (23.8)	2 (3.2)
Pyrexia	10 (15.9)	0
Abdominal pain upper	8 (12.7)	1 (1.6)

- In the delandistrogene moxeparvovec group, **7 patients (11.1%) experienced 10 TR-SAEs** as reported by the PI: acute liver injury† (transient liver enzyme elevations [3 events], hepatotoxicity and liver injury [1 event of each]), myocarditis, nausea, vomiting, pyrexia and rhabdomyolysis (1 event of each).
- The onset of the TR-SAEs were Days 30–51 for acute liver injury, Day 1 for myocarditis, nausea, vomiting and pyrexia, and Day 2 for rhabdomyolysis. **All have resolved.**

*GLDH increases were based on investigator assessment and their institution's normal range. †Terms selected by investigators that refer to similar clinical patterns of liver biochemical markers.

Primary endpoint

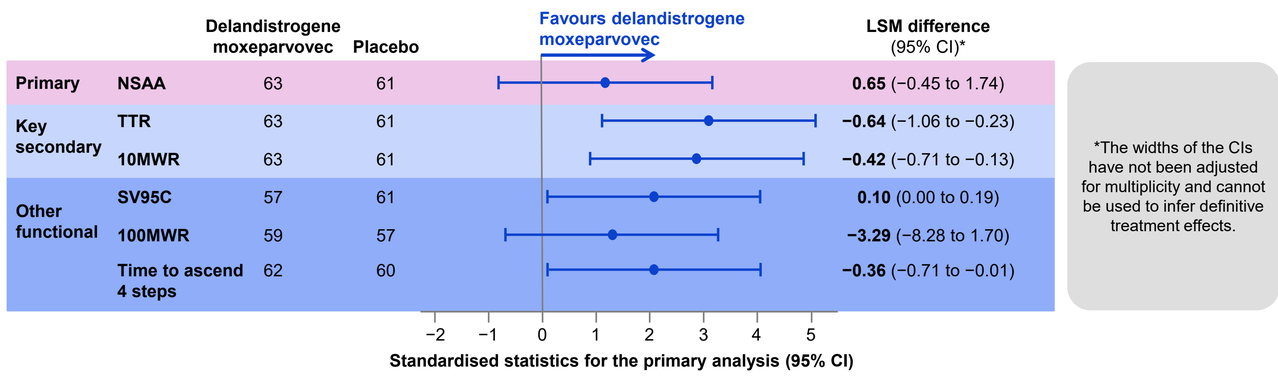
Figure 3. Change from baseline to Week 52 in NSAA total score



*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.

Summary of functional endpoints

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

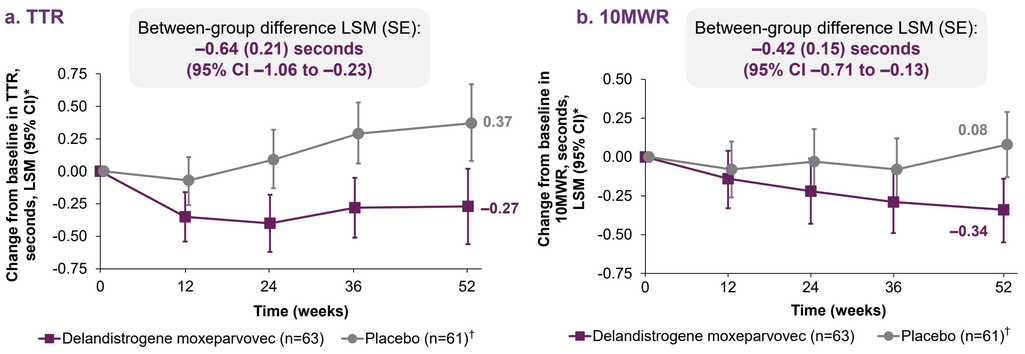


*The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

LSMs (of change from baseline) and CIs were standardised by dividing by the SE. Negative values for TFTs (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 TFTs were reversed in the forest plot to align favourable directions amongst endpoints. Numerical results of LSM difference kept the original signs.

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.**

*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**.

Pre-specified GST

- A pre-specified **GST** was performed as an additional sensitivity 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, time to ascend 4 steps).
- The GST **supported the totality of evidence of treatment effect with delandistrogene moxeparvovec (*P*=0.0044)** and **indicated the presence of a functional treatment effect** after accounting for multiple hypotheses tested across the primary and secondary endpoints.

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.**[19,20]

Patients with TTR >5 seconds at Week 52		Odds ratio (95% CI)
Delandistrogene moxeparvovec (n=63)	Placebo (n=61)	
3.2%	16.4%	**91%** (0.01 to 0.61)

NSAA
- The heterogeneity of DMD disease progression is a challenge when designing trials of short duration in this study population and age range (4- to 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-metre Walk/Run; 100MWR, 100-metre Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; CI, confidence interval; DMD, Duchenne muscular dystrophy; GLDH, glutamate dehydrogenase; GST, global statistical test; ITR, inverted terminal repeat; IV, intravenous; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; OH, hydroxide; PI, principal investigator; polyA, polyadenylation; 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; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event; TTR, Time to Rise.

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Presented at the 29th Annual Congress of the World Muscle Society (WMS), Prague, Czechia; 8–12 October 2024

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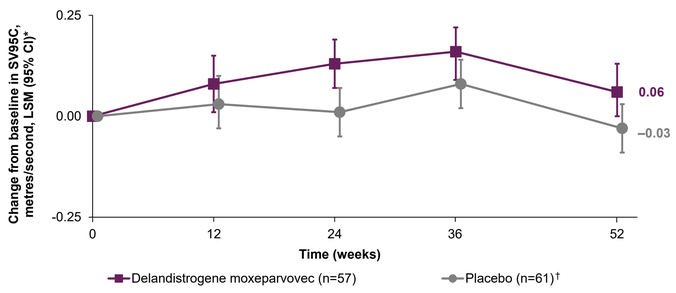
[†]At the time of Part 1 of EMBARK (currently employed by Sarepta Therapeutics, Inc.). *Presenting on behalf of the author group (email address: medinfo@sarepta.com).

SUPPLEMENTARY INFORMATION

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

Between-group difference LSM (SE):
0.10 (0.05) metres/second (95% CI 0.00 to 0.19)



- 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 Week 12, 24, 36 and 52 clinic visits.

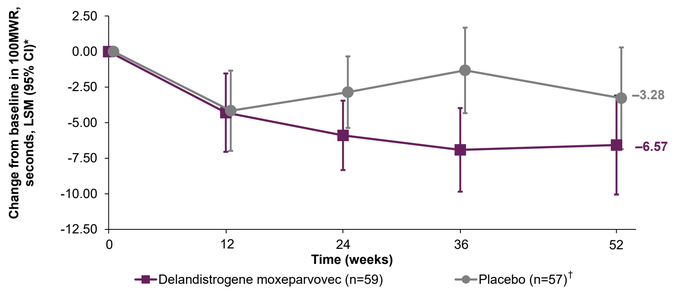
- SV95C is **qualified for use by the EMA as a primary endpoint** in clinical trials of DMD.[1]
- EMBARK is the first randomised, placebo-controlled trial in DMD that **showed clinical relevance of a therapy based on SV95C** from a wearable device.

*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 endpoints
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)

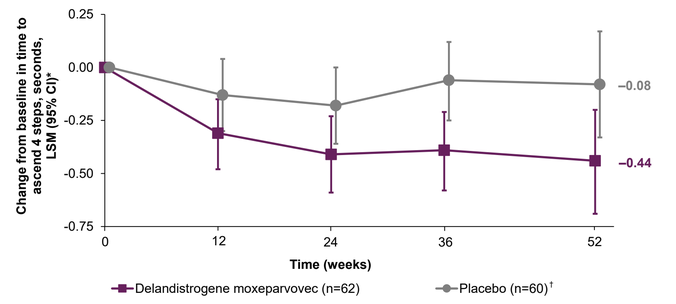
- Negative values indicate an improvement in the time taken to achieve this endpoint.



*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †A small number of tests at either baseline or Week 52 were marked as invalid by the clinical investigator; the most common reason was due to behaviour.

Other secondary functional endpoints
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)

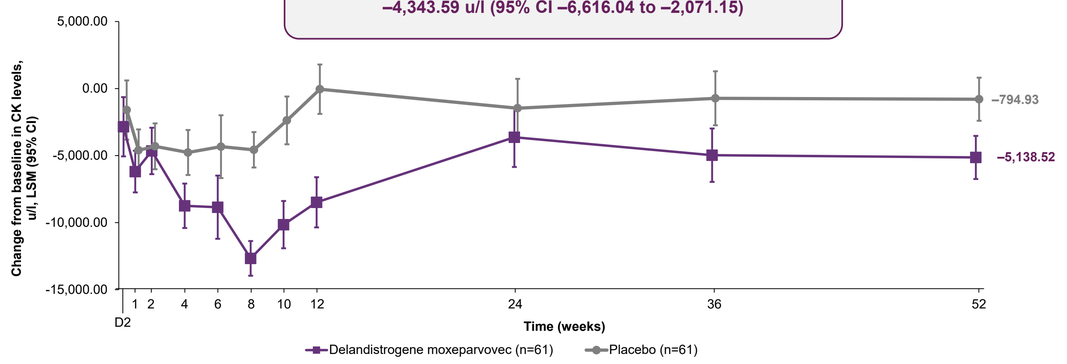


- Negative values indicate an improvement in the time taken to achieve this endpoint.
- The separation between groups was **clinically relevant.**

*The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. †A small number of tests at either baseline or Week 52 were marked as invalid by the clinical investigator; the most common reason was due to behaviour.

Exploratory endpoint
Supplementary Figure 4. Change from baseline to Week 52 in CK levels

Between-group difference LSM:
–4,343.59 u/l (95% CI –6,616.04 to –2,071.15)



Key secondary endpoint
Supplementary Table 1. Delandistrogene moxeparvovec micro-dystrophin expression at 12 weeks post-infusion in a subset of patients*

	Delandistrogene moxeparvovec (n=17)	Placebo (n=14)
Key secondary endpoint		
Western blot (adjusted for muscle content), % normal		
Mean (SD)	34.29 (41.04)	0.00 (0.00)
Median	19.11	0.00

*Baseline data were not available as muscle biopsies were performed only at Week 12. Each patient had two samples of biopsies taken and all samples were analysed.

Other secondary endpoints
Supplementary Table 2. Secondary endpoints (modified intent-to-treat population)

PROMIS mobility	Delandistrogene moxeparvovec (n=60)	Placebo (n=60)
Baseline, mean, score (SD)	4.29 (0.42)	4.20 (0.40)
Week 52, mean, score (SD)	4.31 (0.54) (n=57)	4.21 (0.44) (n=59)
LSM change difference (SE) versus placebo, score; 95% CI	0.05 (0.07); –0.08 to 0.19 (n=57)	N/A
PROMIS upper extremity	**Delandistrogene moxeparvovec (n=60)**	**Placebo (n=59)**
Baseline, mean, score (SD)	3.82 (0.94)	3.60 (0.93)
Week 52, mean, score (SD)	3.98 (0.85) (n=57)	3.90 (0.76) (n=58)
LSM change difference (SE) versus placebo, score; 95% CI	–0.04 (0.10); –0.24 to 0.17 (n=57)	N/A
Number of skills gained or improved at Week 52 as measured by the NSAA	**Delandistrogene moxeparvovec (n=63)**	**Placebo (n=61)***
LSM change (SE), number of skills; 95% CI	4.18 (0.31); 3.58 to 4.79	3.99 (0.31); 3.37 to 4.60
LSM change difference (SE) versus placebo, number of skills; 95% CI	0.19 (0.44); –0.67 to 1.06	N/A

*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. The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

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Abbreviations

100MWR, 100-metre Walk/Run; CI, confidence interval; CK, creatine kinase; Diff, difference; D, day; EMA, European Medicines Agency; LSM, least-squares mean; N/A, not applicable; NSAA, North Star Ambulatory Assessment; PROMIS, Patient-Reported Outcomes Measurement Information System®; SD, standard deviation; SE, standard error; SV95C, stride velocity 95th centile.

Reference

1. European Medicines Agency. Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy_en.pdf (Accessed October 2024).