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

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

What does this study mean for the DMD community?

- **The totality of evidence indicates that delandistrogene moxeparvovec produces potential beneficial disease trajectory modification versus placebo 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

- Safety findings demonstrate the manageable benefit–risk profile of delandistrogene moxeparvovec with no new safety signals identified, and no deaths, study discontinuations or clinically relevant complement-mediated AEs.
- Delandistrogene moxeparvovec did not reach statistical significance compared with placebo in the primary endpoint of NSAA at 52 weeks.
- Between-group differences favoring delandistrogene moxeparvovec on secondary functional endpoints indicate the potential for long-term disease modification of DMD.
- The GST supported the totality of evidence of the beneficial effect of delandistrogene moxeparvovec on motor function.
- A post hoc analysis of TTR showed fewer delandistrogene moxeparvovec-treated patients progressing to a TTR >5 seconds, a prognostic marker for accelerated disease progression and earlier loss of ambulation.

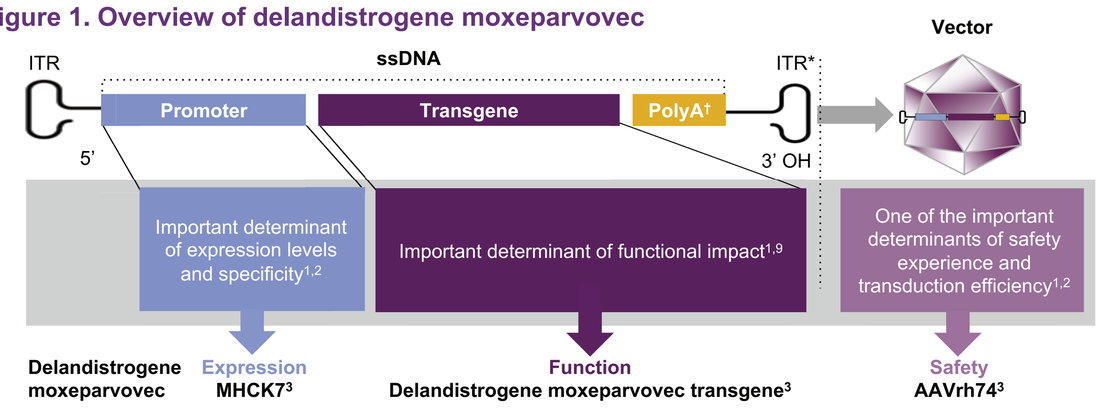
OBJECTIVE

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

BACKGROUND

- Delandistrogene moxeparvovec is a rAAV vector-based gene 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 February 2024, delandistrogene moxeparvovec is approved in the USA, UAE, Qatar and Kuwait 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.[4–7]
- EMBARK (NCT05096221)[8] 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.

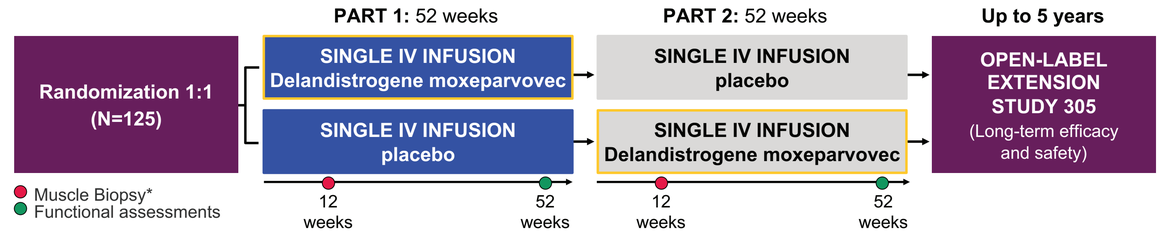
Figure 1. Overview of delandistrogene moxeparvovec



*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[8]

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).

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).

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.[10,11]

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†

*Only a subset of patients will receive a muscle biopsy for expression assessments, based on site experience and feasibility. †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)
Primary and key secondary functional endpoints			
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.

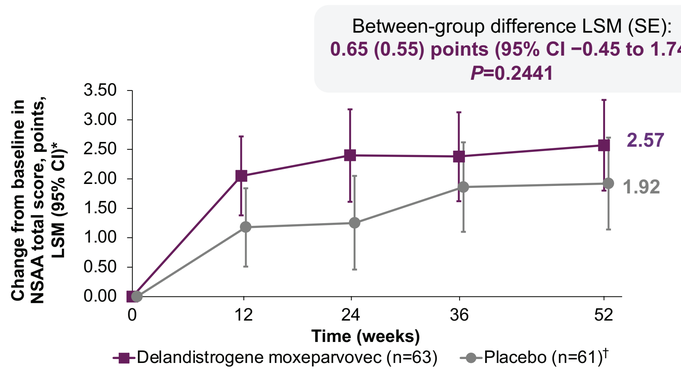
Safety overview

	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**.

Primary endpoint

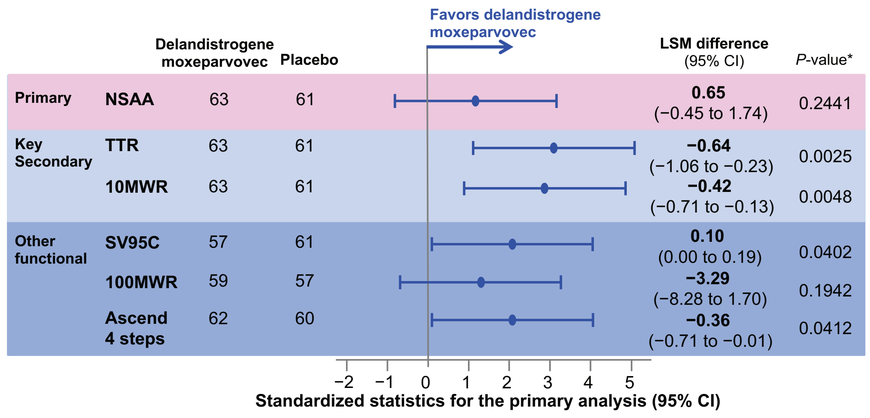
Figure 3. Change from baseline to Week 52 in NSAA total score



*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



*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

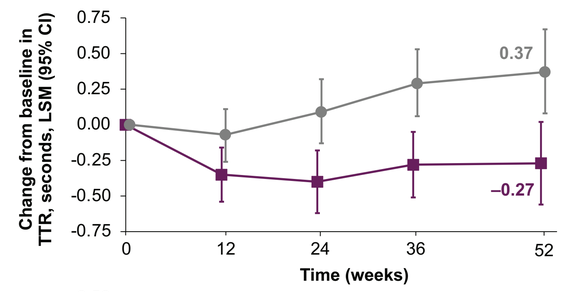
LSMs (of change from baseline) and CIs were standardized by dividing by the SE. Negative values for timed function tests (TTR, 10MWR, 100MWR and time to ascend 4 steps) show an improvement in the time taken to achieve these endpoints. LSM differences are on original scale (without SE adjustment). Signs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

Key secondary functional endpoints

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

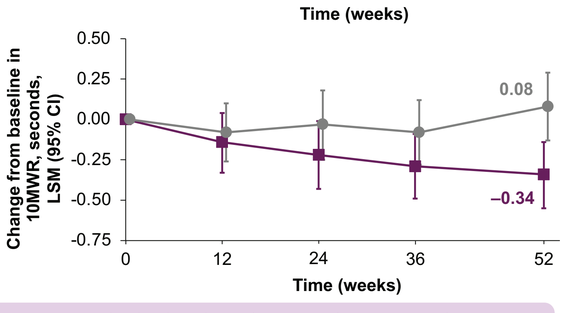
a) TTR

Between-group difference LSM (SE): **–0.64 (0.21) seconds (95% CI –1.06 to –0.23) *P*=0.0025***



b) 10MWR

Between-group difference LSM (SE): **–0.42 (0.15) seconds (95% CI, –0.71, –0.13) *P*=0.0048***



- 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.

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.**[12,13]

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).[14,15]
  - 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.[14] In younger patients, neurodevelopmental maturation might also affect these achievements.[16]

TFTs
- TFTs such as TTR and 10MWR may be more sensitive measures of functional change in this age range and study duration.[14]

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JRM received study funding from Sarepta Therapeutics while at Nationwide Children's Hospital at the time of the study and is currently an employee of Sarepta Therapeutics. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology. FM has received honoraria and grants from Sarepta Therapeutics for participating at symposia and advisory boards and is involved as an investigator in Sarepta Therapeutics clinical trials. He reports participation in advisory boards for Novartis, F. Hoffmann-La Roche Ltd, Edgewise, Dyne Therapeutics, Pfizer, PTC Therapeutics, and Italfarmaco. CMM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfármaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and has a consultancy/advisory role with Biomarin, Capricor, Catalyst, Edgewise, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, and Sarepta Therapeutics. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics. EMM has received fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. EC has received honoraria from Sarepta Therapeutics for participating in advisory boards, and grants as an investigator in Sarepta Therapeutics clinical trials. HK has received grants from Sarepta Therapeutics, Pfizer, PTC Therapeutics, Taiho Pharmaceutical Co. Ltd, Chugai Pharmaceutical Co., Nippon Shinyaku Co. Ltd, and Kaneka Corporation. HK has received fees from Sarepta Therapeutics, Pfizer, PTC Therapeutics, Chugai Pharmaceutical Co., Nippon Shinyaku Co., and Kaneka Corporation. CL-A is an investigator in Sarepta Therapeutics clinical trials and a sub-investigator in studies sponsored by Pfizer, SolidBio, Edgewise, Italfarmaco, and Genentech/Roche. AN has received fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. CP participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; and is a PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock. US-S has received honoraria for counseling and participating in invited talks from Sarepta Therapeutics and F. Hoffmann-La Roche Ltd. AV has a consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, Inc., UCB Pharma, Catalyst, and Scholar Rock; has received research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio, and Sarepta Therapeutics, Inc.; and has other relationship(s) with MedLink Neurology for editorial services. CMZ has received research support from Biogen and Novartis, and has served on an advisory board for Sarepta Therapeutics. MG, CW, and PF are employees of F. Hoffmann-La Roche Ltd and may have stock options. APM and CR are employees of Roche Products Ltd and may have stock options in F. Hoffmann-La Roche Ltd. DRA, ED, SM, RAP, TS, WZ, and JSE are employees of Sarepta Therapeutics and may have stock options. LRR-K is an employee of Sarepta Therapeutics and may have stock options. In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

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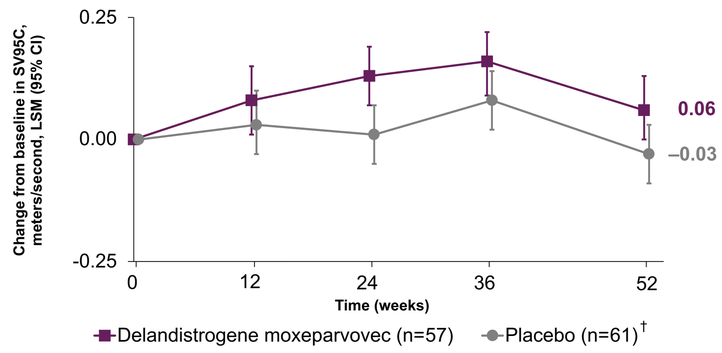
*Presenting on behalf of the author group (email address: medinfo@sarepta.com); [†]At the time of study.

SUPPLEMENTARY INFORMATION

Other secondary functional endpoint:
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



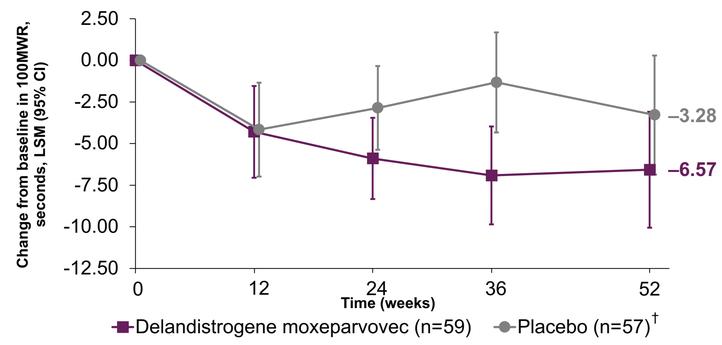
- SV95C is a **digital objective endpoint** of ambulatory performance in patients' **normal daily environment**
- Patients in EMBARK **wore the device on each ankle for 3 weeks** prior to the clinic visits

- 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:
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

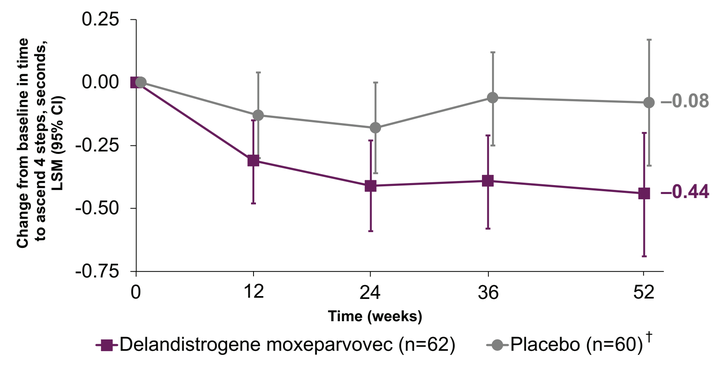


- Negative values indicate an improvement in the time taken to achieve this endpoint

*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 tests at either baseline or Week 52 were marked as invalid by the clinical investigator; the most common reason was due to behavior.

Other secondary functional endpoint:
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**

*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 tests at either baseline or Week 52 were marked as invalid by the clinical investigator; the most common reason was due to behavior.

Study group

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Abbreviations

100MWR, 100-meter Walk/Run; CI, confidence interval; EMA, European Medicines Agency; LSM, least-squares mean; MCID, minimal clinically important difference; SE, standard error; SV95C, stride velocity 95th centile.

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