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

Jerry R. Mendell,*[,1,2,†] Francesco Muntoni,[3] Craig M. McDonald,[4] Eugenio M. Mercuri,[5] Emma Ciafaloni,[6] Hirofumi Komaki,[7] Carmen Leon-Astudillo,[8] Andrés Nascimento,[9] Crystal Proud,[10] Ulrike Schara-Schmidt,[11] Aravindhan Veerapandiyan,[12] Craig M. Zaidman,[13] Maitea Guridi,[14] Alexander P. Murphy,[15] Carol Reid,[15] Christoph Wandel,[14] Damon R. Asher,[16] Eddie Darton,[16] Stefanie Mason,[16] Rachael A. Potter,[16] Teji Singh,[16] Wenfei Zhang,[16] Paulo Fontoura,[14] Jacob S. Elkins,[16] Louise R. Rodino-Klapac[16] on behalf of the EMBARK Study Group

[1]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [2]The Ohio State University, Columbus, OH, USA; [3]The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health and Institute of Neurology, University College London, & Great Ormond Street Hospital Trust, London, UK; [4]UC Davis Health, Sacramento, CA, USA; [5]Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [6]University of Rochester Medical Center, Rochester, NY, USA; [7]Translational Medical Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan; [8]Department of Pediatrics, University of Florida, Gainesville, FL, USA; [9]Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu, CIBERER – ISC III, Barcelona, Spain; [10]Children's Hospital of the King's Daughters, Norfolk, VA, USA; [11]Department of Pediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Essen, University of Duisburg-Essen, Essen, Germany; [12]Department of Pediatrics, Division of Neurology, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR, USA; [13]Department of Neurology, Washington University in St Louis, St Louis, MO, USA; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]Roche Products Ltd, Welwyn Garden City, UK; [16]Sarepta Therapeutics, Inc., Cambridge, MA, USA

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

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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
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- 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 Principal Investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock
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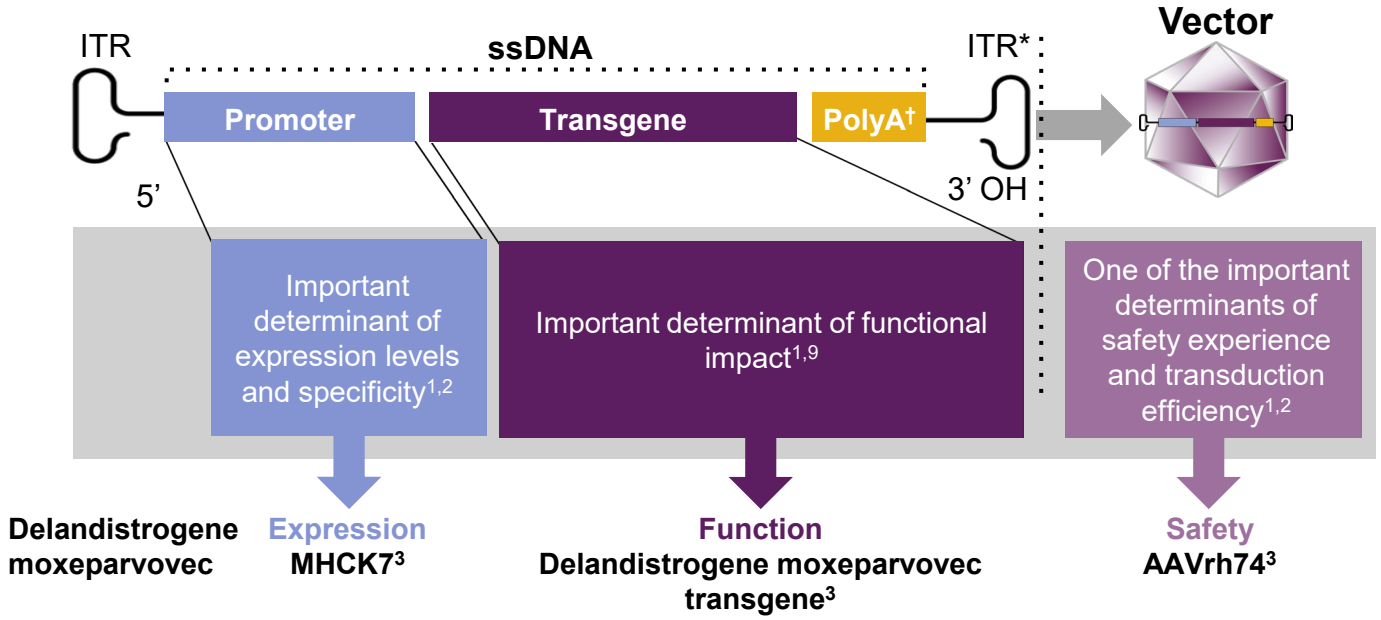
- APM and CR are employees of Roche Products Ltd and may have stock options in F. Hoffmann-La Roche Ltd
- DRA, ED, SM, RAP, TS, WZ, and JSE are employees of Sarepta Therapeutics and may have stock options
- LRR-K is an employee of Sarepta Therapeutics and may have stock options. In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology

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]

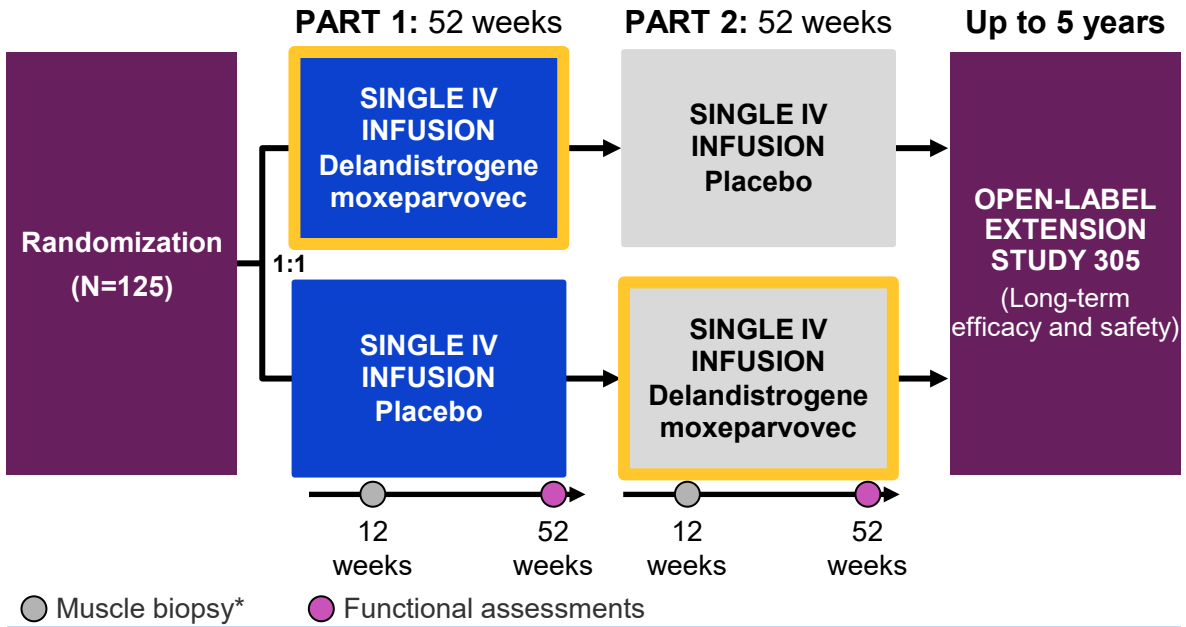
- EMBARK (NCT05096221)[8] is a Phase 3, two-part, multinational, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of delandistrogene moxeparvovec in patients with DMD aged ≥4 to <8 years
- We present an overview of the 1-year safety and functional outcomes from Part 1 of EMBARK



*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.
AAVrh74, adeno-associated virus rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; OH, hydroxide; polyA, polyadenylation; rAAV, recombinant adeno-associated virus; ssDNA, single-stranded DNA.

Study design and endpoints[8]

Stratification based on age at randomization (≥4 to <6 or ≥6 to <8 years) and NSAA total 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 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
- On a stable daily dose of oral corticosteroids for ≥12 weeks before screening
- rAAVrh74 total binding antibody titers <1:400

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.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AE, adverse event; DMD, Duchenne muscular dystrophy; GST, global statistical test; IV, intravenous; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SV95C, stride velocity 95th centile; TEAE, treatment-emergent adverse event; TTR, Time to Rise.

Patient demographics (Part 1)

Demographics 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)
Primary and secondary functional endpoints			
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), meters/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.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; NSAA, North Star Ambulatory Assessment; SD, standard deviation; SV95C, stride velocity 95th centile; TTR, Time to Rise.

Safety overview

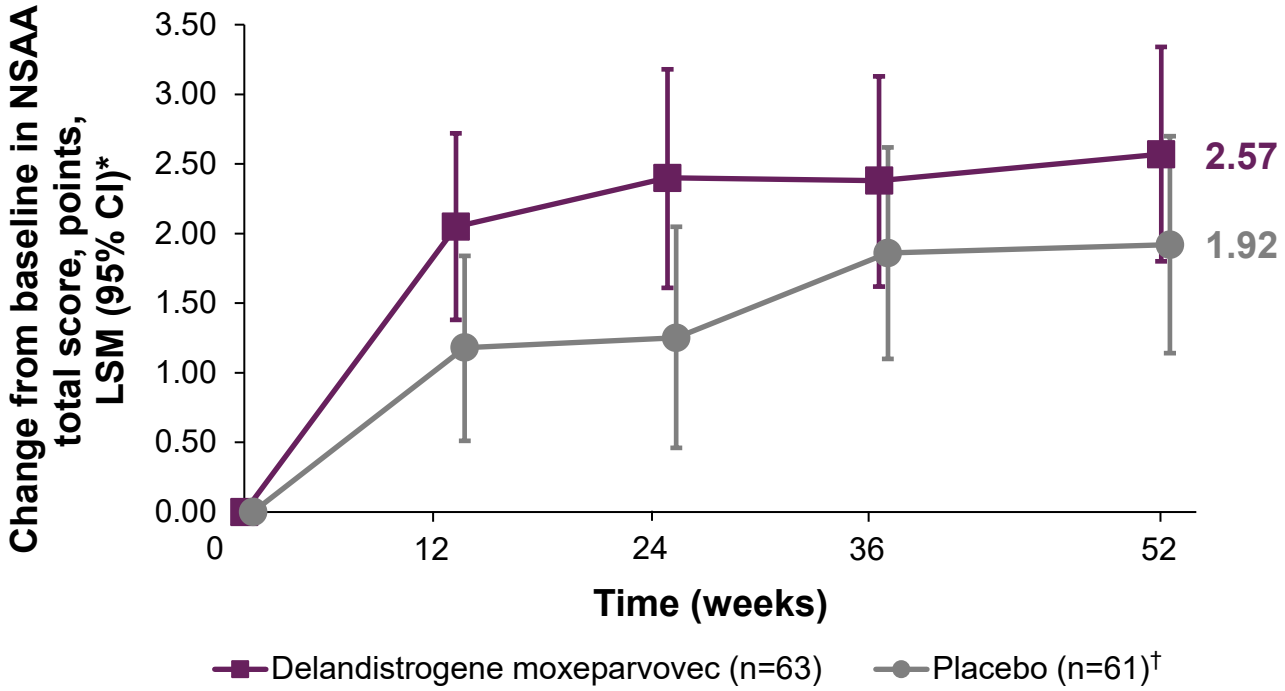
	Delandistrogene moxeparvovec (n=63)	Placebo (n=62)
Patients with any TEAE, n (%)	62 (98.4)	57 (91.9)
TEAEs, n	664	502
Patients with any TR-TEAE, n (%)	48 (76.2)	17 (27.4)
TR-TEAEs, n	235	43
Patients with any TR-SAE, n (%)	7 (11.1)	0
TR-SAEs, n	10	0
Patients with an AE leading to study discontinuation,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

AE, adverse event; TEAE, treatment-emergent adverse event; TR-SAE, treatment-related serious adverse event; TR-TEAE, treatment-related treatment-emergent adverse event.

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

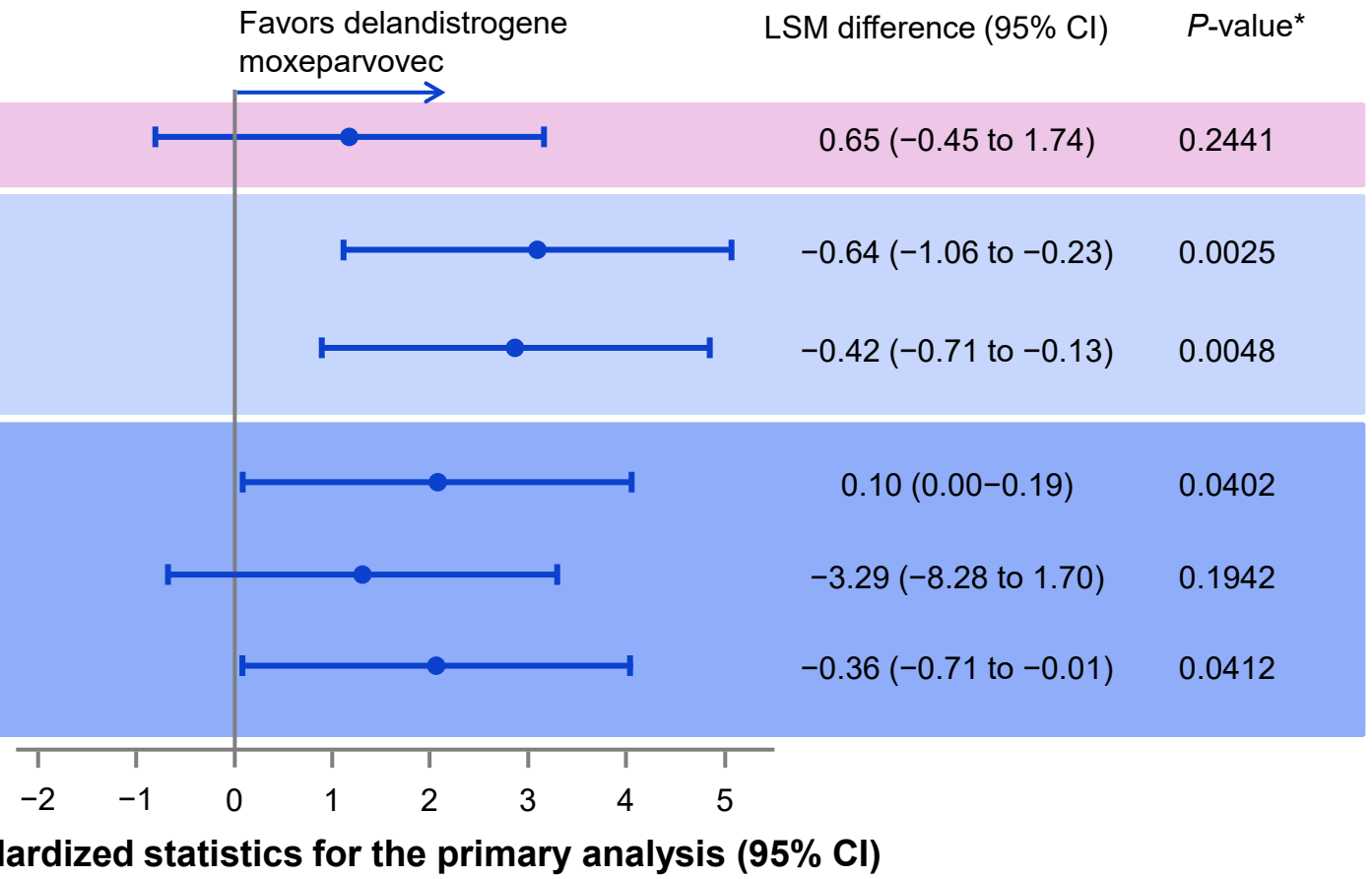
Between-group difference LSM (SE):
0.65 (0.55) points (95% CI −0.45 to 1.74)
***P*=0.2441**



*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.
CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error.

Functional endpoints at Week 52 in the overall population

		Delandistrogene moxeparvovec	Placebo	LSM difference (95% CI)	*P*-value*
Primary	**NSAA**	63	61	0.65 (−0.45 to 1.74)	0.2441
Key secondary	**TTR**	63	61	−0.64 (−1.06 to −0.23)	0.0025
	10MWR	63	61	−0.42 (−0.71 to −0.13)	0.0048
Other functional	**SV95C**	57	61	0.10 (0.00−0.19)	0.0402
	100MWR	59	57	−3.29 (−8.28 to 1.70)	0.1942
	Time to ascend 4 steps	62	60	−0.36 (−0.71 to −0.01)	0.0412

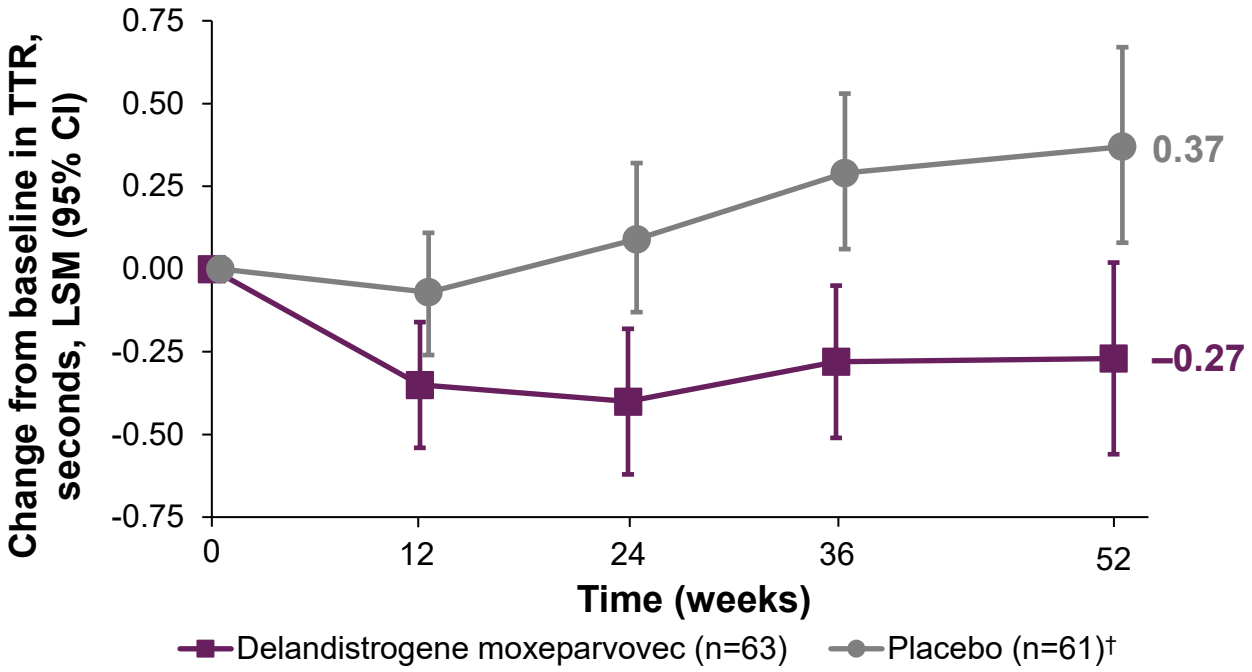


*Since the primary endpoint did not meet statistical significance, all *P*-values resulting from subsequent hierarchical testing are presented with no multiplicity adjustment (nominal). The widths of CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects

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.
10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; CI, confidence interval; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error; SV95C, stride velocity 95th centile; TTR, Time to Rise.

Key secondary functional endpoint: Change from baseline to Week 52 in TTR

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



- 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. †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.
CI, confidence interval; LSM, least-squares mean; SE, standard error; TTR, Time to Rise.

Post hoc analyses on TTR

- All patients had a TTR <5 seconds at screening
- With delandistrogene moxeparvovec treatment, **fewer patients progressed to a TTR of >5 seconds** compared with placebo

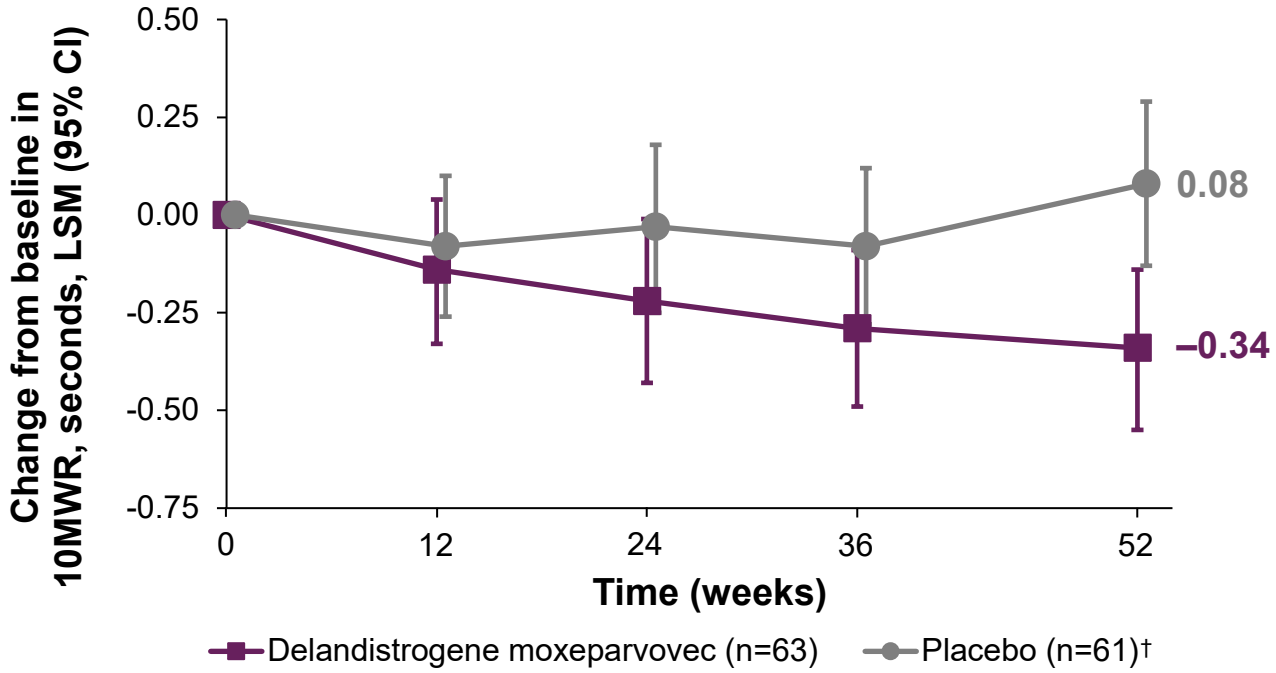
Patients with TTR >5 seconds at Week 52		Reduction in odds
Delandistrogene moxeparvovec (n=63)	Placebo (n=61)	
3%	16%	**91% (*P*=0.0135)**

- A TTR of >5 seconds is a threshold of **prognostic significance for loss of ambulation**[12,13]

TTR, Time to Rise.

Key secondary functional endpoint: Change from baseline to Week 52 in 10MWR

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

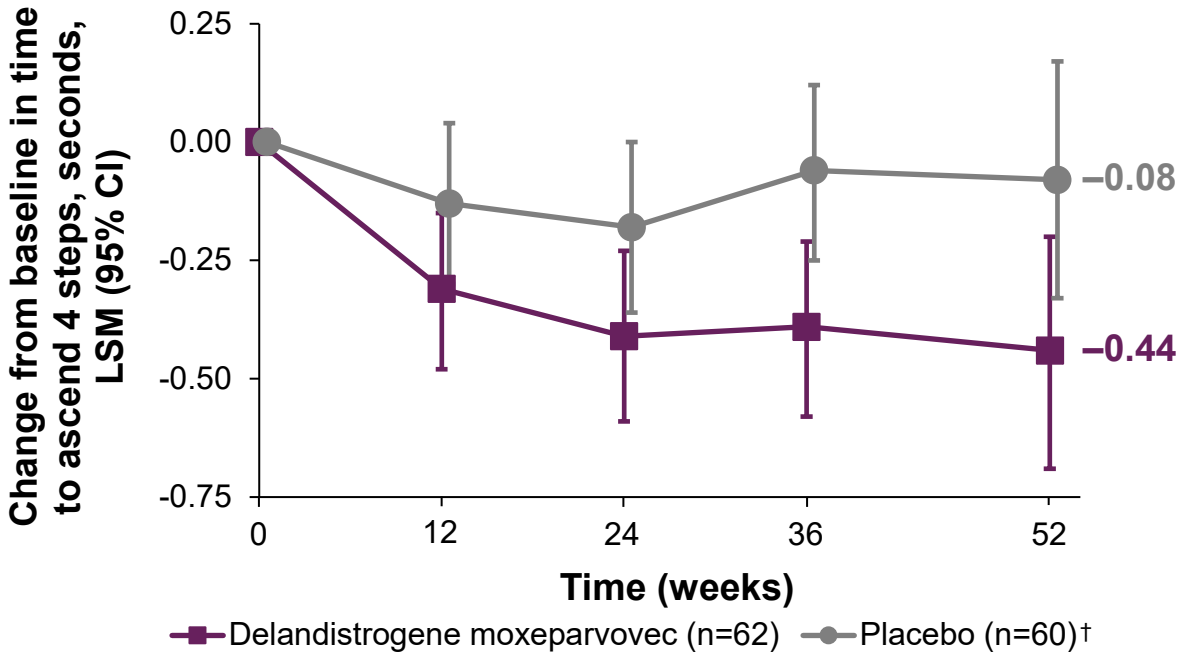


- Negative values indicate an improvement in the time taken to achieve this endpoint
- The separation between groups was **clinically relevant**

*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. †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.
10MWR, 10-meter Walk/Run; CI, confidence interval; LSM, least-squares mean; SE, standard error.

Other secondary functional endpoint: 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.
CI, confidence interval; LSM, least-squares mean; SE, standard error.

Pre-specified global statistical test

- A pre-specified **global statistical test** 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 endpoints: TTR, 10MWR
  - Other secondary endpoints: SV95C, 100MWR, time to ascend 4 steps

The global statistical test **supported the totality of evidence of treatment benefit with delandistrogene moxeparvovec** compared with placebo **(*P*=0.0044)**

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; NSAA, North Star Ambulatory Assessment; SV95C, stride velocity 95th centile; TTR, Time to Rise.

Discussion on functional endpoints

NSAA

- The heterogeneity of DMD disease progression is a challenge in designing trials of short duration in this study population and age range (4- to 7-year-olds)[14,15]
  - Motor function may still be improving, maintaining, or starting to decline
- The NSAA scoring system of 0, 1, or 2 provides only 1-point differences in performance.[14] Trial participants who exhibit only slight difficulty in performance achieve the same score as those barely able to do the task. This results in a score of 1 for both sides, which makes statistical analysis challenging

Timed function tests

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

10MWR, 10-meter Walk/Run; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; TTR, Time to Rise.

Conclusions at Week 52

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 global statistical test 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 of >5 seconds, a prognostic marker for accelerated disease progression and earlier loss of ambulation

- **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 on patients treated in Part 1, allowing progression to be monitored and adding to longer-term data

AE, adverse event; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; TTR, Time to Rise.

EMBARK Study Group

Abe, Yuichi	Chan, Sophelia	Goude, Erica	Kuhn, M. Ann	Nguyen, Bella	Shoemaker, Lawrence
Abbati, Francesca	Chesshyre, Mary	Graham, Michael	Kuntz, Nancy	Nicorici, Alina	Shu, Francy
Ahmadipour, Yahya	Chiriboga, Claudia	Griffin, Danielle	Laine, Regina	Ochiai, Satoru	Sigmund, Shana
Aihara, Tsuyoshi	Chiu, Celine	Guglieri, Michela	Lan Yeung, Wai	Ohashi, Eri	Sivera, Rafael
Alberto, Jorge	Cicala, Gianpaolo	Gurgel, Brittany	Landon, Gregory	Oikawa, Shizuka	Skalsky, Andrew
Alfano, Lindsay	Ciobanu, Teofil	Harmelink, Matthew	Laubscher, Katie	Onodera, Masafumi	Skura, Christy
Alvarez, Maria	Comi, Giacomo Pietro	Harms, Matthew	Laverty, Chamindra	Pane, Marika	Smith, Edward
Apkon, Susan	Connolly, Anne	Harrington, Ann	Leach, Meganne	Panicucci, Chiara	Smith, Erin
Audhya, Ivana	Coratti, Giorgia	Hartzell, Andrea	Lee, Ni-Chung	Panzer, Joseph	Sonehara, Shoko
Awano, Hiroyuki	Cornell, Nikki	Hayakawa, Itaru	Lehman, Kelly	Paola Corti, Stefania	Stanca, Giulia
Baba, Shimpei	Crawford, Thomas	Hicks Wittman, Melissa	Lewis, Sarah	Parsons, Julie	Stechschulte, Mariah
Baek, Ja Yoon	Cripe, Linda	Hirano, Michio	Liang, Wen-Chen	Pasternak, Amy	Stefans, Vikki
Baier, Nele	Cutrona, Costanza	Hoffman, Katie	Liu, Yi-Ching	Patel, Ruchee	Steffens, Paula
Baranello, Giovanni	Dammann, Philipp	Hogan, Mark	Lowes, Linda	Pedemonte, Marina	Straub, Volker
Bartesaghi, Francesca	Darras, Basil	Hoon Lee, Bo	Mackenzie, Samuel	Peiro, Esteban	Strijbos, Paul
Batley, Kaitlin	Day, John	Hor, Kan	Magri, Francesca	Pera, Maria	Sumitomo, Noriko
Benjamin, Robert	Dayan, Jonathan	Hsiu Chien, Yin	Malinova, Monika	Pietro Comi, Giacomo	Surampudi, Prasanth
Berti, Beatrice	De Groote, Katya	Huett, Elizabeth	Manberg, Stephanie	Pietruszewski, Lindsay	Swain, Mary Beth
Blaschek, Astrid	De Sanctis, Roberto	Hustinx, Manon	Markati, Theodora	Pitarch, Inmaculada	Takeshita, Eri
Bloom, Kelsey	De Vivo, Darryl	Hwu, Wuh-Liang	Matesanz, Susan	Poelker, Stephanie	Tesi Rocha, Carolina
Bo, Ryosuke	Deconinck, Nicolas	Iammarino, Megan	Mathews, Katherine	Poon, Freddie	Tokumoto, Shoichi
Bochnak, Meghan	Denecke, Jonas	Iannaccone, Susan	McIntyre, Melissa	Pyzik, Erika	Tomioka, Kazumi
Brandsema, John	Devine, Ginger	Ibanez, Eugenia	McKenzie, Emma	Ramdas, Sithara	Tsuiki, Nobuaki
Branic, Emily	Devos, Daniel	Ignacio Ortez, Carlos	Medina Cantillo, Julita Maria	Rao, Lekha	Vandekerckhove, Kristof
Branigan, Lauren	Driemeyer, Joenna	Iketani, Kiiko	Mei Wan, Yuet	Rao, Vamshi	Vanlander, Arnaud
Braswell, Leah	Eichinger, Katy	Irie, Saeko	Milev, Evelin	Reading, Jacob	Vela, Kerry
Braun, Frederik	El Seed, Maha	Ishido, Mikiko	Miller, Julie	Reash, Natalie F.	Velardo, Daniele
Brolatti, Noemi	ElMallah, Mai	Ishigaki, Keiko	Mockler, Shelley	Ricci, Martina	Vill, Katharina
Brown, Laura	Elrick, Matthew	Ishiguro, Kumiko	Moldt, Sarah	Roca Urraca, Sandra	Waldrop, Megan
Bruno, Claudio	Ennamuri, Sravya	Jackson, Elise	Moody, Yvonne	Saade, Dimah	Warren, Patrick
Brusa, Chiara	Evans, Maya	Janecki, Teresa	Moore Burk, Meghan	Sahenk, Zarife	Watson, Karolina
Burnette, William	Expósito Escudero, Jesica Maria	Johannsen, Jessika	Morando, Simone	Saito, Takashi	Waynick, Anna
Butterfield, Russell	Fassini, Federica	Jong, Yuh Jyh	Motohashi, Yuko	Sampson, Jacinda	Weiss, Deike
Byrne, Barry J.	Finanger, Erika	Katz, Natalie	Moya Arcos, Obdulia	Sato, Takatoshi	Weng, Wen-Chin
Capasso, Anna	Fisher, Gemma	Kelley, Carolyn	Muelas Gomez, Nuria	Schwaede, Abigail	White, Nicole
Carlos Leon, Juan	Fryer, Robert	Khan, Sohrab	Mueller-Felber, Wolfgang	Schwieterman, Jessica	Wilson, Amelia
Carrera Garcia, Laura	Fujii, Saeko	Khounani, Tonya	Murphy, Susan	Scoto, Mariacristina	Wolfe, Amy
Carrera, Laura	Gangfuss, Andrea	Kichula, Elizabeth	Muschol, Nicole	Servais, Laurent	Yamaguchi, Hiroshi
Carry, Terri	Ghafar, Nargies	Kihara, Yuki	Nagase, Hiroaki	Shell, Richard	Yamamoto, Kaoru
Casalini, Sara	Ghimenton, Elisabetta	King-Rennie, Agnes	Nagata, Satoru	Shichiji, Minobu	Yang, Michele
Castro, Diana	Ghosh, Partha	Knox, Renatta	Nambu, Yoshinori	Shieh, Jeng-Yi	Yenzer, Abigail
Cesar Diaz, Sergi	Gilbreath, Heather	Koike, Kentaro	Nance, Jessica	Shieh, Perry	Yu, Lixi
Chagnon, Sarah	Goedeker, Natalie	Kolbel, Heike	Natera de Benito, Daniel	Shih, Hsiang-Hung	Yum, Sabrina
Chan, Nerita	Goelz, Antonia	Koutsogianni, Maria	Nelson, Leslie	Shih, Renata	Zilke, Kirsten

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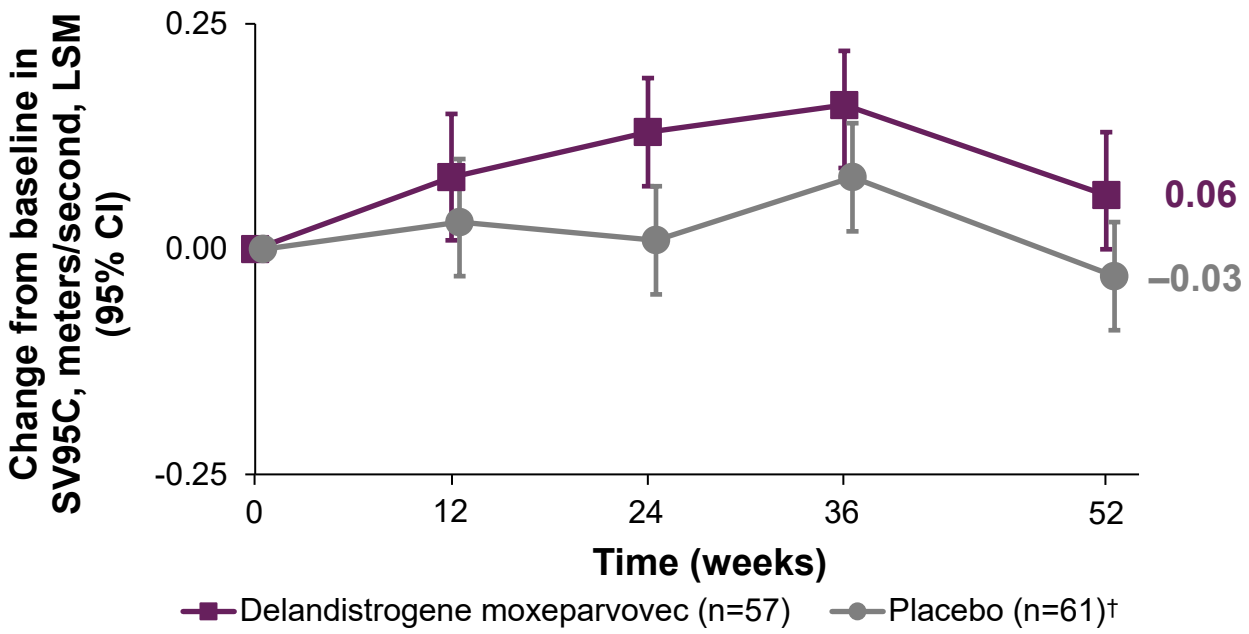
BACKUP

Other secondary functional endpoint: Change from baseline to Week 52 in SV95C

Between-group difference LSM (SE):
0.10 (0.05) meters/second (95% CI 0.00–0.19)
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[16]
- 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.
CI, confidence interval; DMD, Duchenne muscular dystrophy; EMA, European Medicines Agency; LSM, least-squares mean; MCID, minimal clinically important difference; SE, standard error; SV95C, stride velocity 95th centile.

EMBARK RANDOMIZATION AND STRATIFICATION OF NSAA

Pooled Age Group 1	NSAA Total Score at Screening Group	Planned Treatment for Period 01	n
4-5 years old	<= 22	PLACEBO	18
4-5 years old	<= 22	SRP-9001	17
4-5 years old	> 22	PLACEBO	11
4-5 years old	> 22	SRP-9001	13
6-7 years old	<= 22	PLACEBO	12
6-7 years old	<= 22	SRP-9001	10
6-7 years old	> 22	PLACEBO	21
6-7 years old	> 22	SRP-9001	23