EMBARK study design: Phase 3 trial evaluating the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in Duchenne muscular dystrophy

F Muntoni,[1] E Mercuri,[2] U Schara-Schmidt,[3] H Komaki,[4] J Richardson,[5] T Singh,[5] M Guridi,[6] S Mason,[5] A Murphy,[6] L Hu,[5] C Reid,[7] E Darton,[5] C Wandel,[6] JR Mendell[8,9]

[1]The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK; [2]Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [3]Department of Pediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Essen, University of Duisburg-Essen, Essen, Germany; [4]Translational Medical Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan; [5]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]Roche Products Ltd, Welwyn Garden City, UK; [8]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [9]The Ohio State University, Columbus, OH, USA.

What does this study mean for the DMD community?

- EMBARK (Study 301; NCT05096221) is a placebo-controlled study (target enrollment: N=120) assessing the safety and efficacy of commercially representative delandistrogene moxeparvovec (SRP-9001) material in a large population of patients with DMD.

Conclusions

- This study will provide pivotal information about the efficacy and safety of commercially representative delandistrogene moxeparvovec material in a large population of ambulatory patients with DMD.

Objective

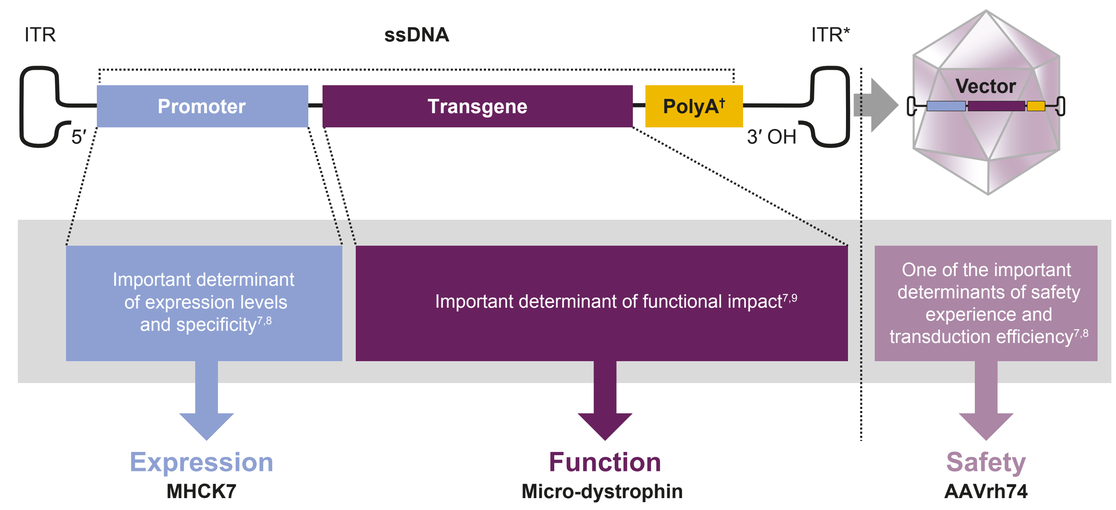
- EMBARK is a Phase 3, global, randomized, double-blind, two-part, placebo-controlled study **to assess the safety and efficacy of delandistrogene moxeparvovec in ambulatory boys with DMD, aged ≥4 to <8 years.**[1]

Background

Delandistrogene moxeparvovec is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of micro-dystrophin—a shortened, functional dystrophin protein (**Figure 1**).[2,3]

- Study 101 (NCT03375164) and Study 102 (NCT03769116)[3–5] demonstrated micro-dystrophin expression in patients with DMD treated with delandistrogene moxeparvovec clinical process material, with no new safety signals identified.
- Results from Cohort 1 of the Phase 1b study ENDEAVOR (Study 103; NCT04626674)[6] demonstrated micro-dystrophin protein expression in ambulatory boys with DMD aged ≥4 to <8 years who were treated with commercially representative delandistrogene moxeparvovec material, with no new safety signals identified.
- EMBARK is a placebo-controlled study assessing the safety and efficacy of commercially representative delandistrogene moxeparvovec material in a larger DMD patient population.

Figure 1. Overview of delandistrogene moxeparvovec (rAAVrh74.MHCK7.micro-dystrophin)



*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 overview

EMBARK is a Phase 3, randomized, double-blind, two-part, placebo-controlled study using commercially representative delandistrogene moxeparvovec material

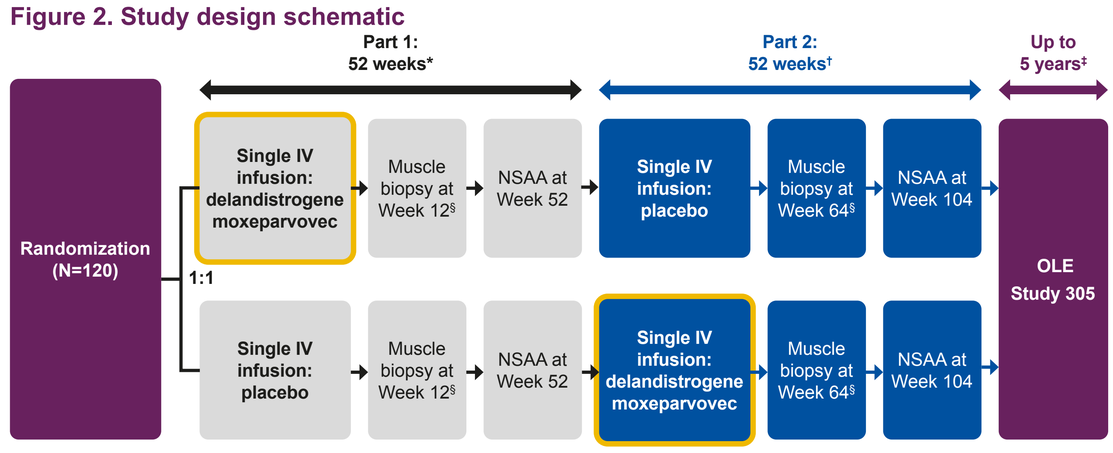
EMBARK is a multinational study to be conducted at ~40 sites in the USA, Europe and Asia.

- Patients will be boys with a confirmed *DMD* mutation, aged ≥4 to <8 years (target enrollment: N=120).
- **Part 1** is a 52-week follow-up period in which patients will be randomized (1:1) to delandistrogene moxeparvovec or placebo (**Figure 2**), according to:
  - age at randomization (≥4 to <8 years)
  - NSAA total score at screening (>16 to <29).
- In Part 1, patients will receive a single, IV 1.33×10^{14} vg/kg (linear standard qPCR) dose of commercially representative delandistrogene moxeparvovec material or placebo.
- **Part 2** is a 52-week crossover follow-up period in which patients who were previously treated with placebo in Part 1 will receive delandistrogene moxeparvovec, and patients who were previously treated with delandistrogene moxeparvovec will receive placebo.
- Study duration: ~108 weeks:
  - pre-infusion period: up to 31 days
  - treatment and follow-up period: 104 weeks.

Key statistical methods

- The primary endpoint and some secondary endpoints will be tested in a hierarchical manner.
- An MMRM analysis will be used to compare the two treatment groups.

Figure 2. Study design schematic



*Double-blind, placebo-controlled. †Patients, caregivers, Investigators and site staff remain blinded. ‡Separate, planned open-label study (Study 305) of up to 5 years post-delandistrogene moxeparvovec infusion. §Only a subset of patients will receive a muscle biopsy for expression assessments.

Study entry criteria and endpoints

Key inclusion criteria

- Ambulatory and aged ≥4 to <8 years at randomization
- Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing
- Confirmed *DMD* mutation within exons 18–44 or 46–79:
  - Participants with mutations between or including exons 1–17 or mutations fully contained within exon 45 (inclusive) are not eligible
  - In-frame deletions, in-frame duplications, and variants of uncertain significance are not eligible
- Ability to cooperate with motor assessment testing
- Stable daily dose of oral corticosteroids for at least 12 weeks prior to screening, and the dose is expected to remain constant throughout the study (except for modifications to accommodate weight changes)
- rAAVrh74 antibody titers are not elevated as per protocol-specified requirements

Additional inclusion criteria apply.

Key exclusion criteria

- Exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression within protocol-specified time limits
- Abnormality in protocol-specified diagnostic evaluations or laboratory tests
- Presence of any other clinically significant illness, medical condition, or requirement for chronic drug treatment that, in the opinion of the Investigator, creates unnecessary risk for gene transfer

Additional exclusion criteria apply.

Primary endpoint

- Change in NSAA total score from baseline to Week 52*

Secondary endpoints

- Number of skills gained or improved at Week 52 as measured by the NSAA*
- Quantity of micro-dystrophin protein expression at Week 12 as measured by WB of biopsied muscle tissue*
- Change from baseline to Week 52 in TFTs: time to rise from the floor, 100MWR, time to ascend 4 steps, and 10MWR*
- Change in SV95C from baseline to Week 52 as measured by Syde®, a wearable device*
- Change in PROMIS score per domain (mobility and upper extremity function) from baseline to Week 52*
- Incidence of treatment-emergent AEs, SAEs and AEs of special interest; clinically significant changes in vital signs, physical examination findings, safety laboratory assessments, ECGs and ECHOs

*Part 1.

Abbreviations

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AE, adverse event; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ITR, inverted terminal repeat; IV, intravenous; MHCK7, myosin heavy chain kinase 7; MMRM, mixed model for repeated measures; NSAA, North Star Ambulatory Assessment; OH, hydroxide; OLE, open-label extension; polyA, polyadenylation; PROMIS, Patient-Reported Outcomes Measurement Information System; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant adeno-associated virus serotype rh74; SAE, serious AE; ssDNA, single-stranded DNA; SV95C, Stride Velocity 95th Centile; TFT, timed function test; vg, vector genomes; WB, western blot.

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Acknowledgments

We would like to thank the patients and their families for participation in this study, as well as the investigators and trial staff involved in EMBARK. This study is sponsored by Sarepta Therapeutics and funded by Sarepta Therapeutics and F. Hoffmann-La Roche. Writing and editorial assistance was provided by Jen Ciarochi, PhD, of Nucleus Global, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3). FM has received honoraria from Sarepta for participating at symposia and advisory boards, and he is involved as an investigator in Sarepta clinical trials. EM receives fees from AveXis, Biogen and F. Hoffmann-La Roche. US-S receives honoraria for counseling and invited talks from Sarepta and Roche. HK has received honoraria from Sarepta for participating in advisory boards, and grants and honoraria for invited talks and consulting for Chugai Pharmaceutical Co. JR, TS, SM, LH and ED are employees of Sarepta Therapeutics and may have stock options. MG, AM, CR and CW are employees of F. Hoffmann-La Roche and may have stock options. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

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Presented at the Muscular Dystrophy Association (MDA) In-Person or Virtual Clinical and Scientific Conference, March 13–16, 2022