Poster 100

EMBARK, a Phase 3 trial evaluating safety and efficacy of delandistrogene moxeparvovec in DMD: Study design and baseline characteristics

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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 intended commercial process delandistrogene moxeparvovec (SRP-9001) material in a large population of patients with DMD.

Conclusions

- EMBARK will provide placebo-controlled data on the safety and efficacy of intended commercial process delandistrogene moxeparvovec material in a large population of ambulatory patients with DMD aged ≥4 to <8 years.

Objective

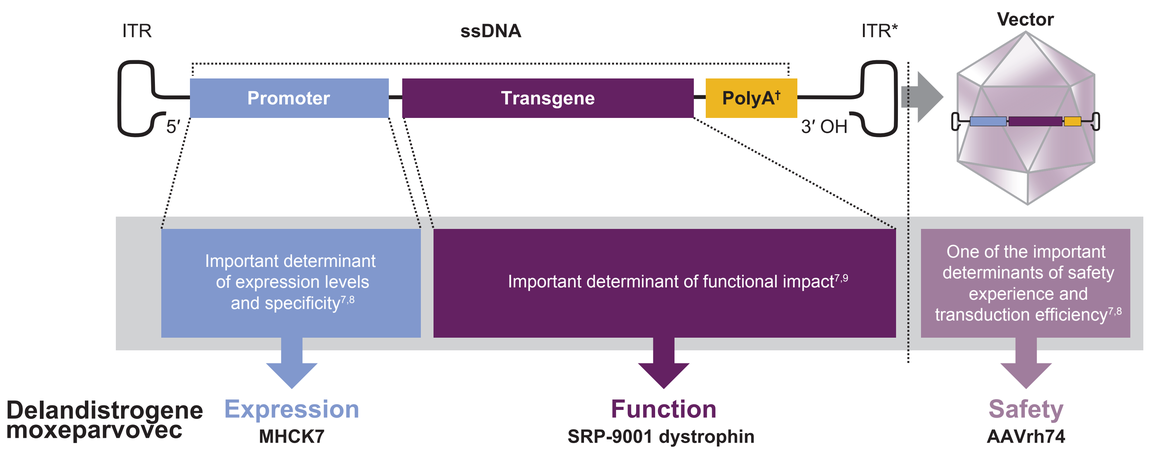
- To describe the study design and baseline patient characteristics of EMBARK[1], an ongoing Phase 3, global, randomized, double-blind, two-part, placebo-controlled study assessing the safety and efficacy of intended commercial process delandistrogene moxeparvovec material.

Background

Delandistrogene moxeparvovec is an investigational rAAV vector-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding SRP-9001 dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein (**Figure 1**).[2,3]

- Study 101 (SRP-9001-101; NCT03375164) and Study 102 (SRP-9001-102; NCT03769116)[3–5] demonstrated SRP-9001 dystrophin expression in patients with DMD treated with delandistrogene moxeparvovec clinical process material, with no new safety signal identified.
- Results from Cohort 1 of the Phase 1b study ENDEAVOR (Study 103; NCT04626674)[6] demonstrated SRP-9001 dystrophin protein expression in ambulatory boys with DMD aged ≥4 to <8 years who were treated with intended commercial process delandistrogene moxeparvovec material, with no new safety signals identified.

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

EMBARK is a Phase 3, randomized, double-blind, two-part, placebo-controlled study using intended commercial process delandistrogene moxeparvovec material

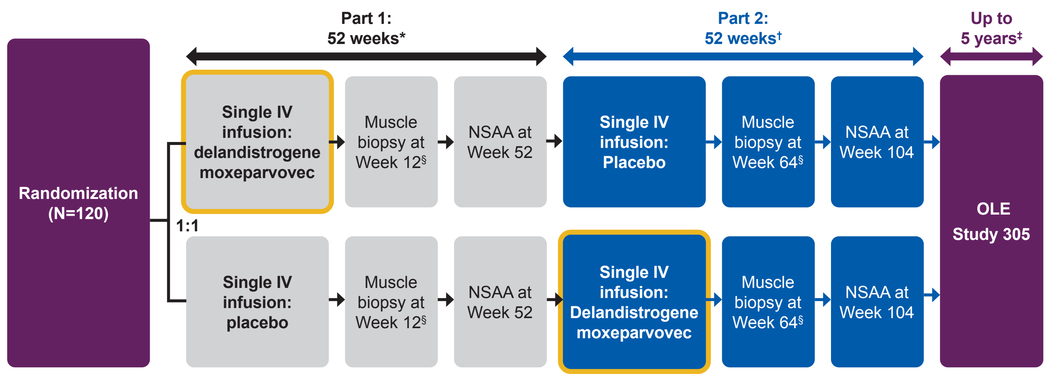
EMBARK is a multinational study to be conducted at ~40 sites in the USA, Europe, and Asia.

- 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 the following two stratification factors:
  - Age at randomization (≥4 to <6 years or ≥6 to <8 years)
  - NSAA total score at screening (≤22 points or >22 points).
- In Part 1, patients will receive a single IV $1.33x10^{14}$ vg/kg (linear standard qPCR) dose of intended commercial process delandistrogene moxeparvovec material or placebo.
- **Part 2** is a blinded 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 (**Figure 2**).
- 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 secondary endpoints will be tested in a hierarchical manner.
- An MMRM analysis will be used to analyze all secondary endpoints except SRP-9001 dystrophin expression, which will use a re-randomization test.

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 fully contained between exons 18 to 79 (inclusive) that is expected to lead to the absence of dystrophin protein:
  - 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.
- NSAA score at time of screening (>16 and <29).
- TTR at time of screening (<5 seconds).
- 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 inclusion 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 (Part 1)
- Quantity of SRP-9001 dystrophin protein expression at Week 12 as measured by WB of biopsied muscle tissue*
- Change from baseline to Week 52 in TFTs: TTR, 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

Results

Baseline demographics*

Baseline characteristics	EMBARK study (N=126)
Age, years	
Mean (SD), Min–max	5.5 (1.05) 4–7
Age group, n (%)	
4–5	62 (49.2)
6–7	64 (50.8)
Race, n (%)	
White	93 (71.8)
Black or African American	2 (1.6)
Asian	20 (15.9)
Multiple	1 (0.8)
Not reported	6 (4.8)
Other	4 (3.2)
Ethnicity, n (%)	
Hispanic or Latino	23 (18.3)
Not Hispanic or Latino	100 (79.4)
Not reported	2 (1.6)
Unknown	1 (0.8)

*Age and age group are based on age at screening.

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; 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; rAAV, recombinant adeno-associated virus; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; ssDNA, single-stranded DNA; SV95C, Stride Velocity 95th Centile; TFT, timed function test; vg, vector genomes; WB, western blot.

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Acknowledgments and disclosures

The authors would like to thank the patients and their families for their participation in EMBARK, as well as the investigators and trial staff involved in EMBARK. This study is sponsored by Sarepta Therapeutics, Inc., Cambridge, MA, USA and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing and editorial assistance were provided by Ayesha Babar, MSc, of Nucleus Global, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and were funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland. FM has received honoraria from Sarepta Therapeutics for participating at symposia and advisory boards, and he is involved as an investigator in Sarepta Therapeutics clinical trials. EM receives fees from AveXis, Biogen and F. Hoffmann-La Roche Ltd. US-S receives honoraria for counseling and invited talks from Sarepta Therapeutics and F. Hoffmann-La Roche Ltd. HK has received honoraria from Sarepta Therapeutics for participating in advisory boards, and grants and honoraria for invited talks and consulting for Chugai Pharmaceutical Co. JR, TS, SM, LY and ED are employees of Sarepta Therapeutics and may have stock options. MG, APM, and CW are employees of F. Hoffmann-La Roche Ltd. and have nothing to disclose. CR is an employee of Roche Products Ltd and holds stock in F. Hoffman-La Roche Ltd. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics 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) Clinical and Scientific Conference, Dallas, TX, USA, March 19−22, 2023