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 (SRP-9001-301; NCT05096221)[1] is a placebo-controlled study assessing the safety and efficacy of commercial process delandistrogene moxeparvovec material in a large population of ambulatory patients with DMD, aged ≥4 to <8 years (N=126).

Conclusion

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

Objective

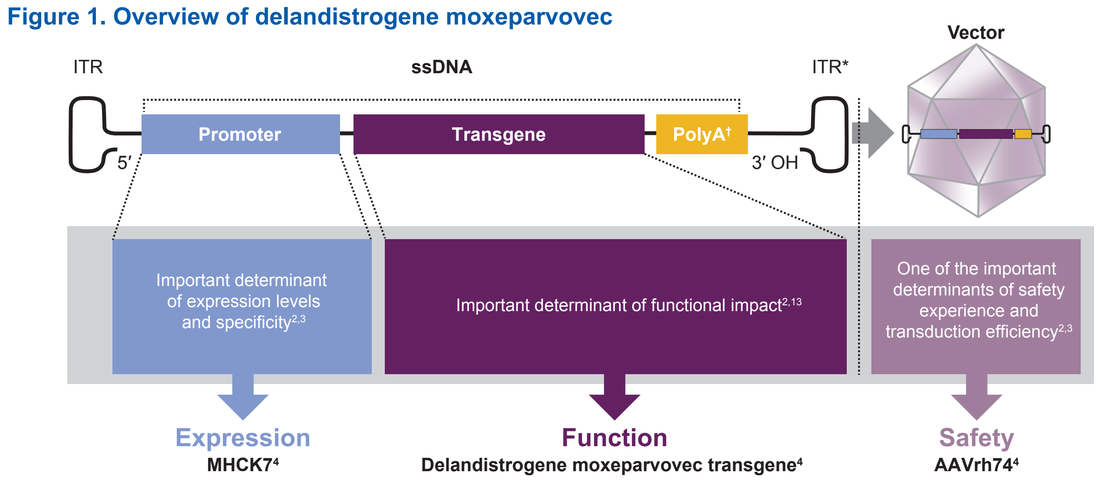
- To describe the study design and baseline patient characteristics of EMBARK, an ongoing Phase 3, global, randomized, double-blind, two-part, placebo-controlled study assessing the safety and efficacy of commercial process delandistrogene moxeparvovec.

Background

- Delandistrogene moxeparvovec is an 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 (**Figure 1**).[2–4]
- Delandistrogene moxeparvovec is approved in the USA and UAE for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.[5,6*†]
- Study 101 (SRP-9001-101; NCT03375164): Results demonstrated improvement in NSAA score and a favorable safety profile up to 4 years following treatment with delandistrogene moxeparvovec, in patients with DMD aged ≥4 to <8 years.[4,7,8]
- Study 102 (SRP-9001-102; NCT03769116): Findings support a favorable benefit–risk profile. Overall stabilization of motor function was observed up to 2 years following treatment with delandistrogene moxeparvovec, in patients with DMD aged ≥4 to <8 years. Robust delandistrogene moxeparvovec micro-dystrophin expression and sarcolemmal localization were demonstrated up to 60 weeks post-treatment, confirming transduction efficiency of the delandistrogene moxeparvovec transgene to target cells.[9,10]
- Findings from Cohort 1 of the ENDEAVOR study (SRP-9001-103; NCT04626674) suggest similar clinical benefit from the commercial process delandistrogene moxeparvovec material as has been observed in previous studies utilizing clinical process material.[11,12]

*Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene. †As of August 2023.

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 commercial process delandistrogene moxeparvovec material

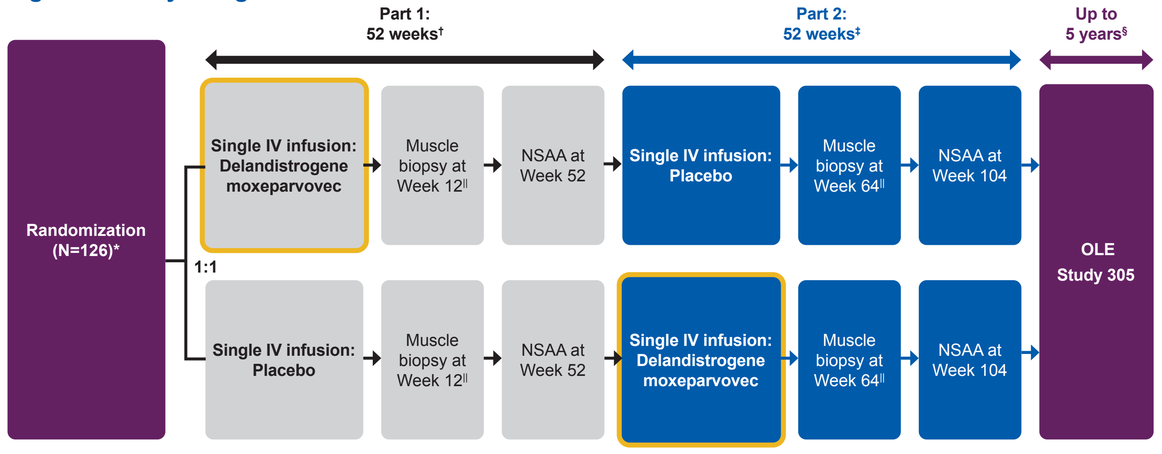
EMBARK is a multinational study to be conducted at ~40 sites in the USA, Europe, and Asia.

- Patients will be male with a confirmed *DMD* mutation, aged ≥4 to <8 years (N=126).
- Study duration: ~108 weeks:
  - Pre-infusion period: up to 31 days
  - Treatment and follow-up period: 104 weeks.
- **Part 1** is a 52-week follow-up period in which patients will be randomized (1:1) to delandistrogene moxeparvovec or placebo, 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 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**).

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 delandistrogene moxeparvovec micro-dystrophin expression, which will use a re-randomization test.

Figure 2. Study design schematic



*N=120 was the target recruitment. †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 exclusion criteria apply.

Primary endpoint

- Change in NSAA total score from baseline to Week 52 (Part 1)

Secondary endpoints

- Quantity of delandistrogene moxeparvovec micro-dystrophin expression at Week 12 as measured by WB of biopsied muscle tissue (Part 1)
- Change from baseline to Week 52 in TFTs: TTR, 100MWR, time to ascend 4 steps, and 10MWR (Part 1)
- Change in SV95C from baseline to Week 52 as measured by a wearable device (Part 1)
- Change in PROMIS score per domain (mobility and upper extremity function) from baseline to Week 52 (Part 1)
- Number of skills gained or improved at Week 52 as measured by the NSAA (Part 1)
- 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

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; AAVrh74, adeno-associated virus rhesus isolate serotype 74; 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, hydroxyl; 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; TTR, Time to Rise; UAE, United Arab Emirates; vg, vector genome; WB, western blot.

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