ENVOL, a Phase 2, open-label trial evaluating the safety and expression of delandistrogene moxeparvovec in patients with Duchenne muscular dystrophy aged <4 years: Study design

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What does this study mean for the DMD community?

- ENVOL (EudraCT Number: 2022-000691-19)[1] will provide data on the safety and transduction efficiency of delandistrogene moxeparvovec in a population of younger patients (aged <4 years) with DMD.

Conclusions

- ENVOL will assess delandistrogene moxeparvovec gene therapy in patients aged <4 years, complementing the patient population studied in the delandistrogene moxeparvovec clinical trials to date: across the patient journey from early ambulatory to late non-ambulatory.
- Investigation in the pediatric population will fill a scientific gap and allow for the evaluation of early therapeutic intervention, dose, safety, and efficacy, and the potential to improve the long-term prognosis in pediatric patients with DMD.
- The novel Elecsys® anti-rAAVrh74 assay will be used for the first time in ENVOL.

Objective

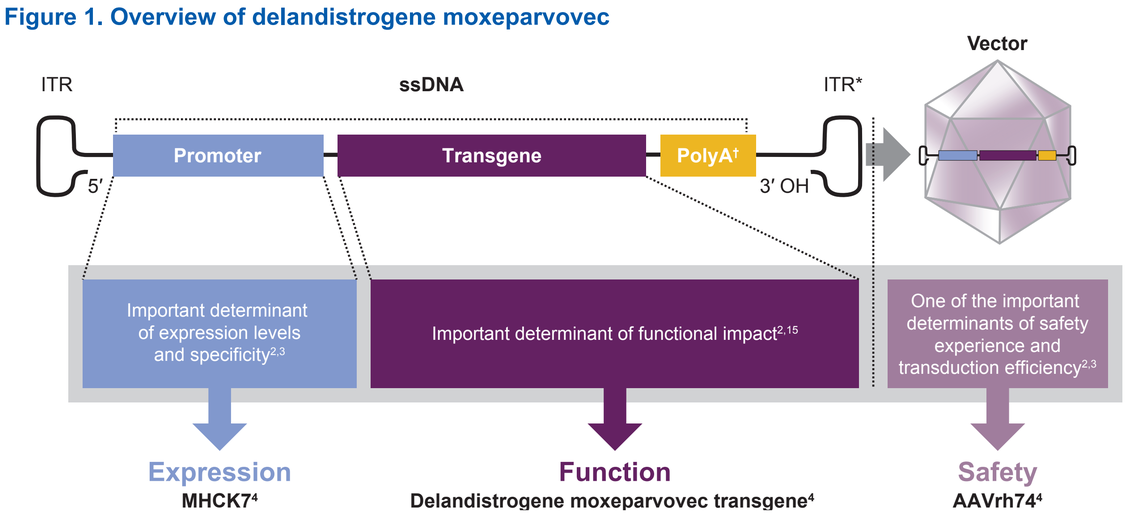
- To describe the study design of ENVOL, a Phase 2, open-label, multi-cohort, two-part study assessing the safety and transduction efficiency of delandistrogene moxeparvovec in patients aged <4 years with a confirmed *DMD* mutation between exons 18 and 79.

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 for up to 2 years following treatment with delandistrogene moxeparvovec in patients 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 to that observed in previous studies utilizing clinical process material.[11,12]
- EMBARK (SRP-9001-301; NCT05096221) is an ongoing, international, Phase 3 study to evaluate the safety and efficacy of delandistrogene moxeparvovec in ambulatory patients aged ≥4 to <8 years.[13]
- ENVISION (SRP-9001-303; NCT05881408) will evaluate the safety and efficacy of delandistrogene moxeparvovec in non-ambulatory (no age restriction) and late-ambulatory (aged ≥8 to <18 years) patients with DMD, a population not yet investigated in a large pivotal clinical trial.[14]

*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



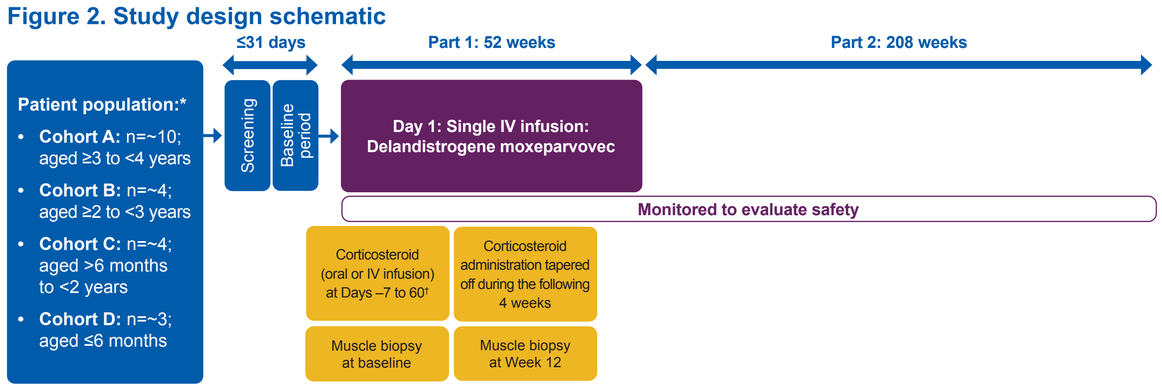
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.

Study design

ENVOL is an open-label, single-arm, two-part study to evaluate the safety and transduction efficiency of systemic gene therapy with commercial process delandistrogene moxeparvovec material in male patients with DMD aged 0 to <4 years (target enrollment: ~21 patients).

- In **Part 1** (52-week follow-up), Cohorts A−D will receive a single IV 1.33×10^{14} vg/kg dose of delandistrogene moxeparvovec.
- In **Part 2** (208-week follow-up), patients will be monitored to evaluate safety (**Figure 2**).

Figure 2. Study design schematic



*At the time of signing the Informed Consent form, participants should be approximately 1 month younger than the maximum age to qualify for a cohort that is actively enrolling to ensure that cohort-specific age criteria are met at the time of dosing. †Baseline period begins once eligibility is confirmed and starts 7 days before delandistrogene moxeparvovec infusion on Day 1.

Eligibility

Key inclusion criteria*

- Male with a diagnosis of DMD.
- Confirmed *DMD* mutation fully contained between exons 18 to 79 (inclusive) (mutations between or including exons 1—17, in-frame deletions, in-frame duplications, and VUS will be excluded).
- rAAVrh74 antibody levels not elevated as determined by the Elecsys® anti-rAAVrh74 assay.
- Able to cooperate with age-appropriate motor assessment testing.
- Parent(s) or legal guardian(s) able to understand and comply with the study visit schedule and all protocol requirements.

*Additional inclusion criteria apply.

Key exclusion criteria*

- Receiving regular oral corticosteroids as a treatment for DMD or planning to receive oral corticosteroids as a treatment for DMD within 1 year of baseline.
- Major surgery within 3 months prior to Day 1 or planned surgery during Part 1.
- Presence of any other clinically significant illness, medical condition, or requirement for chronic drug treatment that creates unnecessary risk for gene therapy.
- LVEF <50% on the screening ECHO or clinical signs/symptoms of cardiomyopathy.
- Symptomatic infection within 4 weeks prior to Day 1.
- Exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression within protocol-specified time limits.
- Abnormal laboratory values considered clinically significant.
- Cohorts A and B: Current, chronic, or active HIV, hepatitis C, or hepatitis B infection.
- Cohorts C and D: Serological evidence of HIV, hepatitis B, or hepatitis C infection, as determined by the patient's mother.
- Cohorts C and D: Premature birth or relevant pregnancy complications.

*Additional exclusion criteria apply.

Endpoints

Primary endpoints

- Incidence of treatment-emergent AEs, SAEs, and AEs of special interest
- Clinically significant changes in vital signs and physical examination findings
- Clinically significant changes in safety laboratory assessments, ECGs, and ECHOs

Secondary endpoint

Change in quantity of delandistrogene moxeparvovec micro-dystrophin expression from baseline to Week 12 as measured by WB

Exploratory endpoints*

- Change from baseline to Week 12 in delandistrogene moxeparvovec micro-dystrophin expression, as measured by immunofluorescence fiber intensity and immunofluorescence PDPF
- Vector genome copies assessed using ddPCR in serum and muscle tissue biopsy
- Functional assessments: From 3 years of age, NSAA, 10MWR, TTR, and timed 4-stair Climb; from 4 years of age, 100MWR
- Change in normalized score in the Bayley IV gross motor and fine motor domains in Cohorts B, C, and D (for Cohort D, baseline is the first assessment after the patient has reached 6 months of age)
- Change in CK from baseline
- Changes in serum concentrations of exploratory biomarkers of efficacy, disease progression, pathophysiology, and safety from baseline
- Change in musculoskeletal MRI findings from 4 years of age and then annually
- Change from baseline (defined as first assessment after the patient has reached 3 years of age) in an ambulation assessment, as measured by a wearable device: SV95C
- Change in normalized score in the Bayley IV cognition and language domains in Cohorts B, C, and D (for Cohort D, baseline is the first assessment after the patient has reached 6 months of age)
- Immunogenicity of delandistrogene moxeparvovec as assessed by ELISA to rAAVrh74 antibodies and the delandistrogene moxeparvovec transgene

*Additional exploratory endpoints apply.

Statistical analyses

- The analysis of safety (primary endpoint) will be performed for each cohort after all patients in the cohort have completed or withdrawn from Part 1 (Week 52) of the study, and data will be summarized descriptively by cohort.
- The final analysis will be performed when all participants have completed or withdrawn from Part 2 (Week 260).
- For Cohort A, the change from baseline to Week 12 in delandistrogene moxeparvovec micro-dystrophin expression (secondary endpoint) will be summarized descriptively and analyzed using a Wilcoxon signed-rank test at the two-sided 5% significance level; for Cohorts B, C, and D, the observed values and change from baseline values for muscle biopsy endpoints will be summarized descriptively for each cohort.
- All exploratory endpoints will be summarized descriptively.

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Abbreviations

10MWR, 10-meter Walk/Run; 100MWR, 100-meter Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; CK, creatine kinase; ddPCR, droplet digital polymerase chain reaction; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; ITR, inverted terminal repeat; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance image; NSAA, North Star Ambulatory Assessment; OH, hydroxyl; PDPF, percent dystrophin-positive fibers; PolyA, polyadenylation; rAAV, recombinant adeno-associated virus; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; ssDNA, single-stranded DNA; SV95C, Stride Velocity 95th Centile; TTR, Time to Rise; UAE, United Arab Emirates; vg, vector genome; VUS, variant of uncertain significance; WB, western blot.

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