ENVISION, a Phase 3, randomized trial evaluating the safety and efficacy of delandistrogene moxeparvovec in Duchenne muscular dystrophy: Study design

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What does this study mean for the DMD community?

- ENVISION (SRP-9001-303; NCT05881408)[1] 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. Safety, biological and clinical endpoints will be measured in Part 1 (72 weeks) and Part 2 (crossover period; 52 weeks): patients who are randomized to placebo in Part 1 will have the opportunity for treatment with delandistrogene moxeparvovec in Part 2. After completion of Part 2, patients will be eligible to enroll into an extension study to assess long-term safety and efficacy for at least 5 years after delandistrogene moxeparvovec infusion.[2]

Conclusion

- ENVISION will allow for evaluation of the safety and efficacy of delandistrogene moxeparvovec, as assessed by measures of physical, respiratory, and cardiac function in a large multinational population of both non-ambulatory (no age restriction) and late-ambulatory (aged ≥8 to <18 years) patients with DMD, a population not yet investigated in a large randomized, double-blind, placebo-controlled clinical trial.

Objective

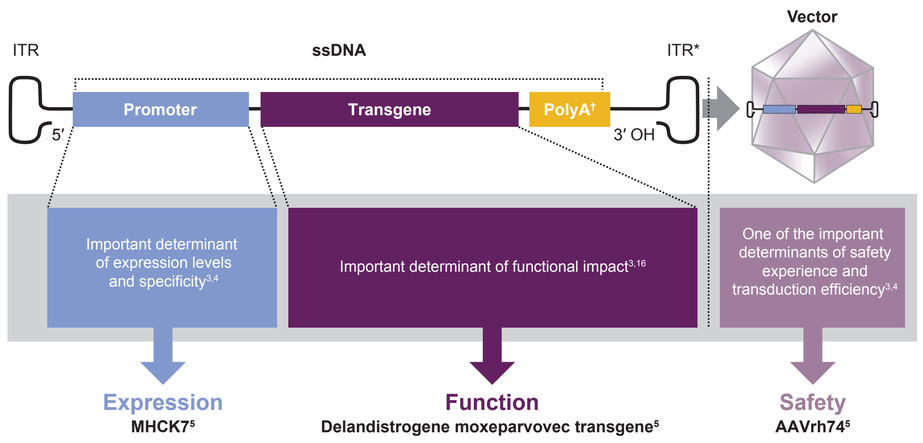
- To evaluate the safety and efficacy of delandistrogene moxeparvovec, as measured by physical, respiratory, and cardiac function; and micro-dystrophin expression in non-ambulatory (no age restriction) and late-ambulatory (aged ≥8 to <18 years) patients with DMD.

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**).[3–5]
- 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.[6,7,*,†]
  - 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.[5,8,9]
  - 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 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.[10,11]
  - 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.[12,13]
  - 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.[14]
  - ENVOL (EudraCT Number: 2022-000691-19) is 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.[15]

*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.

Eligibility

Key inclusion criteria*

- Confirmed genetic diagnosis of DMD.†
- A pathogenic frameshift mutation within the *DMD* gene or premature stop codon contained between exons 18 and 79 (inclusive).
- Cohort 1 (non-ambulatory;‡ PUL entry item score ≥3 and total PUL score ≥20 and ≤40 at screening).
- Cohort 2 (late-ambulatory, ≥8 to <18 years of age; PUL entry item score >3 and <6, total PUL score of ≥20 and ≤40, and NSAA score ≥12 and ≤26 at screening).
- Able to cooperate with motor assessment testing.
- rAAVrh74 antibody titers <1:400 (not elevated; as determined by a total binding antibody ELISA).
- On a stable dose of oral corticosteroids (≥12 weeks before screening). Note that no use of corticosteroids is considered a stable dose (i.e. 0 mg).

Key exclusion criteria*

- Presence of LVEF <40% or clinical signs and/or symptoms of cardiomyopathy.
- FVC <40% of the predicted value at screening.
- Presence of any other clinically significant illness.§
- Serological evidence of infection‖ or symptomatic infection within 4 weeks of the day of infusion.
- Demonstrates cognitive delay or impairment that could confound motor development.
- Treatment with any of the following therapies: gene therapy, cell-based therapy, CRISPR/Cas9, or any other gene editing treatment at any time; use of HGF or vamorolone within 12 weeks prior to the day of infusion and anytime during the study; treatment with any investigational medication or any treatment designed to increase dystrophin expression within 6 months of the day of infusion and anytime during the study (e.g. exon-skipping therapy, ataluren).
- Abnormal laboratory tests for GGT, GLDH,¶ total bilirubin, WBC, or platelet count.

*Additional inclusion and exclusion criteria apply. †Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice mutation, or other pathogenic variant in the *DMD* gene fully contained between exons 18 and 79 (inclusive) that is expected to lead to complete absence of dystrophin protein. Mutations fully or partially contained between exons 1 and 17 (inclusive) are not eligible. ‡Has been non-ambulatory for a minimum of 6 months, with onset of non-ambulatory status defined as participant- or caregiver-reported age at continuous wheelchair use, approximated to the nearest month, an NSAA walk score of "0", and the inability to perform the 10MWR at the screening visit. §Including cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or infection, malignancy, concomitant illness, or requirement for chronic drug treatment that, in the opinion of the Investigator, creates unnecessary risks for gene therapy, or a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the patient's ability to comply with the protocol-required testing or procedures or compromise the patient's wellbeing, safety, or clinical interpretability. ‖Has serological evidence of current, chronic, or active HIV, hepatitis C, or hepatitis B infection. ¶GLDH testing criterion is for ex-USA only.

Endpoints

Primary endpoint*

- Change in PUL (V2.0) total score from baseline to Week 72 (Part 1)

Secondary endpoints*

- Change in FVC% predicted and PEF% predicted from baseline to Week 72 (Part 1)
- Quantity of delandistrogene moxeparvovec micro-dystrophin expression as measured by WB at Week 12 (Part 1)
- Change in PROMIS® score in Upper Extremity Function from baseline to Week 72 (Part 1)
- For Cohort 2 only: Change in the NSAA score from baseline to Week 72 (Part 1)
- Incidence of TEAEs, AEs of special interest, SAEs, clinically significant changes in vital signs, physical examination findings, safety laboratory assessments, ECGs, and ECHOs
- Change in global circumferential strain by cMRI from baseline to Week 72 (Part 1)

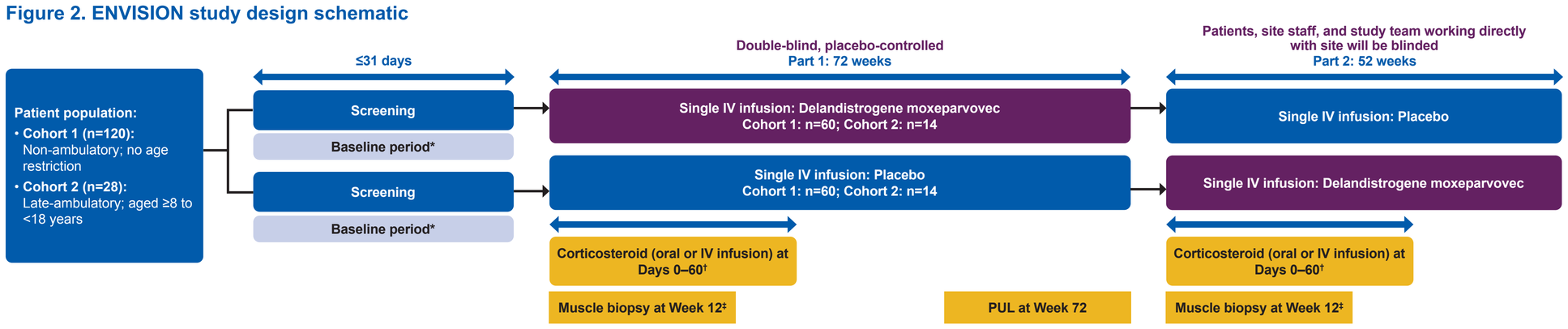
*Additional exploratory endpoints apply.

Study design

ENVISION is a Phase 3, multinational (North America, Europe, Asia, Australia), randomized, double-blind, two-part, placebo-controlled study of systemic gene therapy of delandistrogene moxeparvovec in ~148 patients across two cohorts over ~128 weeks:

- Cohort 1 consists of ~120 non-ambulatory male patients with DMD (no age restriction).
- Cohort 2 consists of ~28 late-ambulatory male patients with DMD who are aged ≥8 to <18 years.

Figure 2. ENVISION study design schematic



*Baseline period begins when eligibility is confirmed. †Starting the day prior to the infusion, all patients will receive corticosteroids (prednisone equivalent) for at least 60 days after the infusion unless earlier tapering is required to manage an AE. ‡Only a subset of patients will receive a muscle biopsy assessment.

Statistical analyses

- The primary and secondary efficacy endpoints will be tested in a hierarchical manner using an appropriate multiple-testing approach.
- Efficacy analyses will be performed separately by cohort.
- A restricted maximum likelihood-based MMRM analysis will be used to compare the two treatment groups.
- Descriptive statistics will be provided for AEs and other safety endpoints by treatment group.

Abbreviations

10MWR, 10-meter walk/run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; Cas9, CRISPR-associated protein 9; cMRI, cardiac magnetic resonance imaging; CRISPR, clustered regularly interspaced short palindromic repeats; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; ELISA, enzyme-linked immunosorbent assay; FVC, forced vital capacity; GLDH, glutamate dehydrogenase; GGT, gamma-glutamyl transferase; HGF, human growth factor; HIV, human immunodeficiency virus; ITR, inverted terminal repeat; IV, intravenous; LVEF, left ventricular ejection fraction; MMRM, mixed model for repeated measures; NSAA, North Star Ambulatory Assessment; OH, hydroxyl; PEF, peak expiratory flow; PolyA, polyadenylation; PROMIS, Patient-Reported Outcomes Measurement Information System; PUL, Performance Upper Limb; rAAV, recombinant adeno-associated virus; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SAE, serious adverse event; ssDNA, single-stranded DNA; TEAE, treatment-emergent adverse event; UAE, United Arab Emirates; WB, western blot; WBC, white blood cell.

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