Delandistrogene Moxeparvovec Gene Therapy in Ambulatory Patients (Aged ≥4 to <8 Years) with Duchenne Muscular Dystrophy: 1-Year Interim Results from Study SRP-9001-103 (ENDEAVOR)

Craig M. Zaidman, MD,[1] Crystal M. Proud, MD,[2] Craig M. McDonald, MD,[3] Kelly J. Lehman, FNP, PPC-MHS,[4] Natalie L. Goedeker, CPNP,[1] Stefanie Mason, MD, MPH,[5] Alexander P. Murphy, MD, PhD,[6] Maitea Guridi, PhD,[7] Shufang Wang, PhD,[5] Carol Reid, PhD,[6] Eddie Darton, MD, JD,[5] Christoph Wandel, MD, PhD,[7] Sarah Lewis, HT, ASCP,[5] Jyoti Malhotra, PhD,[5] Danielle A. Griffin, MBA,[5] Rachael A. Potter, PhD,[5] Louise R. Rodino-Klapac, PhD,[5] and Jerry R. Mendell, MD[4,8]

Objective: Delandistrogene moxeparvovec is approved in the USA for the treatment of ambulatory patients (4–5 years) with Duchenne muscular dystrophy. ENDEAVOR (SRP-9001-103; NCT04626674) is a single-arm, open-label study to evaluate delandistrogene moxeparvovec micro-dystrophin expression, safety, and functional outcomes following administration of commercial process delandistrogene moxeparvovec.
Methods: In cohort 1 of ENDEAVOR (N = 20), eligible ambulatory males, aged ≥4 to <8 years, received a single intravenous infusion of delandistrogene moxeparvovec (1.33×10^{14} vg/kg). The primary endpoint was change from baseline (CFBL) to week 12 in delandistrogene moxeparvovec micro-dystrophin by western blot. Additional endpoints evaluated included: safety; vector genome copies; CFBL to week 12 in muscle fiber-localized micro-dystrophin by immunofluorescence; and functional assessments, including North Star Ambulatory Assessment, with comparison with a propensity score-weighted external natural history control.
Results: The 1-year safety profile of commercial process delandistrogene moxeparvovec in ENDEAVOR was consistent with safety data reported in other delandistrogene moxeparvovec trials (NCT03375164 and NCT03769116). Delandistrogene moxeparvovec micro-dystrophin expression was robust, with sarcolemmal localization at week 12; mean (SD) CFBL in western blot, 54.2% (42.6); $p < 0.0001$. At 1 year, patients demonstrated stabilized or improved North Star Ambulatory Assessment total scores; mean (SD) CFBL, +4.0 (3.5). Treatment versus a propensity score-weighted external natural history control demonstrated a statistically significant difference in least squares mean (standard error) CFBL in North Star Ambulatory Assessment, +3.2 (0.6) points; $p < 0.0001$.

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Address correspondence to Dr Craig M. Zaidman, Department of Neurology, Washington University in St. Louis, 660 S Euclid Ave, St. Louis, MO 63108, USA. E-mail: zaidmanc@wustl.edu

From the [1]Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA; [2]Children's Hospital of the King's Daughters, Norfolk, VA, USA; [3]University of California Davis Health, Sacramento, CA, USA; [4]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [5]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [6]Roche Products Ltd, Welwyn Garden City, UK; [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland; and [8]The Ohio State University, Columbus, OH, USA

Interpretation: Results confirm efficient transduction of muscle by delandistrogene moxeparvovec. One-year post-treatment, delandistrogene moxeparvovec was well tolerated, and demonstrated stabilized or improved motor function, suggesting a clinical benefit for patients with Duchenne muscular dystrophy.

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Duchenne muscular dystrophy (DMD) is an X-linked, neuromuscular disease caused by mutations in the *DMD* gene that prevent the production of functional dystrophin. This loss of function leads to progressive muscle weakness and shortened life expectancy.[1-4] Corticosteroids can reduce symptoms and slow disease progression,[5,6] but are associated with significant side effects and do not address the underlying cause of DMD[7]—lack of functional dystrophin.[1] Gene therapies aim to address the underlying cause of disease by delivering a therapeutic transgene to target tissue.[8] Delandistrogene moxeparvovec is approved in the USA for the treatment of ambulatory pediatric patients aged 4 to 5 years with DMD with a confirmed mutation in the *DMD* gene.[9] It is a recombinant adeno-associated viral (rAAV) vector-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered protein that retains key functional domains of the wild-type dystrophin.[10] Delandistrogene moxeparvovec micro-dystrophin includes actin-binding and cysteine-rich domains; spectrin-like repeats R1 to 3, which confer membrane-binding ability and protect muscle by modulating radial force transmission and mechanical vulnerability; spectrin-like repeat R24, a domain important for microtubule organization; and hinges 1, 2, and 4, which are short, proline-rich spacers providing elasticity to the protein.[11-15] Expression of the delandistrogene moxeparvovec transgene is under control of the MHCK7 promoter, which is associated with robust expression in skeletal muscle, including the diaphragm.[16-18] MHCK7 includes an enhancer that preferentially drives expression in the heart, while preventing transcription in off-target tissues.[16]

Delandistrogene moxeparvovec is delivered through a single intravenous administration and utilizes the rAAV rhesus isolate serotype 74 (rAAVrh74) vector, selected for its safety profile, tropism to the muscle, and low prevalence of pre-existing immunity.[10] Pre-existing humoral immunity to viral vectors can impact the safety and efficacy of gene therapies.[19,20] Encouragingly, a study of 101 patients with DMD demonstrated very little pre-existing immunity to rAAVrh74, with 86.1% (87/101, 95% confidence interval [CI] 77.8–92.2) of those patients testing seronegative, which is defined as antibody titers ≤1:400.[21] The ≤1:400 antibody threshold is based on studies in non-human primates that found no inhibition of transduction or safety events with titers at or below this level; these findings were subsequently validated in human trials.[19]

Delandistrogene moxeparvovec is currently being evaluated in a comprehensive clinical development program that includes four studies.[22–25] Initially, delandistrogene moxeparvovec was manufactured in small quantities as a clinical process material for use in the small numbers of patients participating in trials SRP-9001-101 (NCT03375164; active, not recruiting; estimated study completion date: April 30, 2023) and SRP-9001-102 (NCT03769116; active, not recruiting; estimated study completion date: April 2, 2026). To accommodate larger pivotal clinical trials and prepare for potential commercial use following approval by regulatory bodies, a commercial process delandistrogene moxeparvovec material that is suitable for large-scale production was developed.

ENDEAVOR (Study SRP-9001-103; NCT04626674) is a study to assess the expression of delandistrogene moxeparvovec micro-dystrophin, safety, and motor function following a single administration of commercial process delandistrogene moxeparvovec material in seven independent cohorts of patients with DMD. Here, we report interim, 1-year results from ENDEAVOR cohort 1, comprised of 20 ambulatory patients, aged ≥4 to <8 years. Additionally, to contextualize functional results in patients treated with delandistrogene moxeparvovec, we utilize a rigorous, well-matched natural history control cohort, obtained from external sources, for comparative analysis.

Methods

Manufacturing

The delandistrogene moxeparvovec product is manufactured using the following process. Three plasmids (the delandistrogene moxeparvovec transgene expression cassette, AAV capsid genes, and helper adenovirus genes) are co-transfected to HEK293 cells. The three plasmids plus the adenoviral E1 genes in HEK293 cells provide necessary and sufficient elements to produce a large quantity of the virus rAAVrh74.MHCK7.micro-dystrophin. The virus is purified and formulated into a solution to result in delandistrogene moxeparvovec.

Two manufacturing processes (A and B) were utilized in the clinical program. Process A, designed as an early development manufacturing process, was used in early-stage clinical trials (SRP-9001-101 and SRP-9001-102) at Nationwide Children's Hospital (Ohio State

University, Columbus, OH, USA). Process B, used in SRP-9001-103 and the ongoing phase 3 EMBARK trial, is well designed and controlled for its intended purpose of late-stage clinical material and commercial production. This process utilizes a scaled-up purification method that incorporates chromatography-based methods for separation of the empty capsid residuals from the full capsids. Although the two processes are not analytically comparable with respect to the empty to full capsid ratio, the clinical results are comparable, including expression, safety, and function (see Table 2 and Fig. 17 from the United States FDA Cellular, Tissue and Gene Therapies Advisory Committee, May 12, 2023 sponsor briefing document, as part of the accelerated approval of delandistrogene moxeparvovec).[26]

Study Design and Participants

ENDEAVOR is a two-part, open-label, phase 1b study of systemic delivery of commercial process delandistrogene moxeparvovec material. The total study duration is 264 weeks, inclusive of an up to 31-day pre-infusion period and a 260-week post-treatment follow-up period. There is a target enrollment of approximately 58 participants across the seven cohorts (Fig 1). Here, we report 1-year data from cohort 1 (N = 20), enrolled across four sites in the USA, from November 2020 to April 2021 (data cut-off date May 2022). Key inclusion criteria at screening were: ambulatory patients aged ≥4 to <8 years; North Star Ambulatory Assessment (NSAA) total score >17 and ≤26; confirmed genetic diagnosis of DMD with mutations (frameshift deletion/duplication, nonsense, canonical splice site mutation, or other pathogenic variant) between exons 18 and 79 (inclusive); indication of symptomatic muscular dystrophy (creatine kinase elevation >1,000 U/L and <95% predicted time on 100-meter Walk/Run [100MWR]); on a stable baseline dose of oral corticosteroids for ≥12 weeks before screening; and total antibody titers to rAAVrh74 ≤1:400 (clinically determined to be "not elevated"). Other ENDEAVOR cohorts (patients with mutations between exons 18 and 79, inclusive, as described above), results from which will be reported elsewhere, are: cohort 2 (N = 7, ambulatory patients, aged ≥8 to <18 years); cohort 3 (N = 6, non-ambulatory patients of all ages); cohort 4 (N = 7, ambulatory patients, aged ≥3 to <4 years); cohort 6 (target N = 6, ambulatory patients, aged ≥2 to <3 years); and cohort 7 (target N = 4 to 6, non-ambulatory patients). As it became evident that deletions including exons 9 to 13 were associated with immune-mediated myositis,[27] it was expected that the benefit–risk profile for patients with other mutations in exons 1 to 17 would be similar to that for those with mutations fully contained between exons 18 and 79. This led to the addition of cohort 5, which includes patients with mutations in the region of exons 1 to 17, but not those with deletion mutations in exons 9 to 13. Cohort 5 (N = 8) consists of two subgroups: 5a (N = 6, ambulatory patients, aged ≥4 to <9 years) and 5b (N = 2, non-ambulatory patients of all ages). Patients exposed to gene therapy at any time or any treatment designed to increase dystrophin expression within 6 months of day 1 were excluded. Additional exclusion

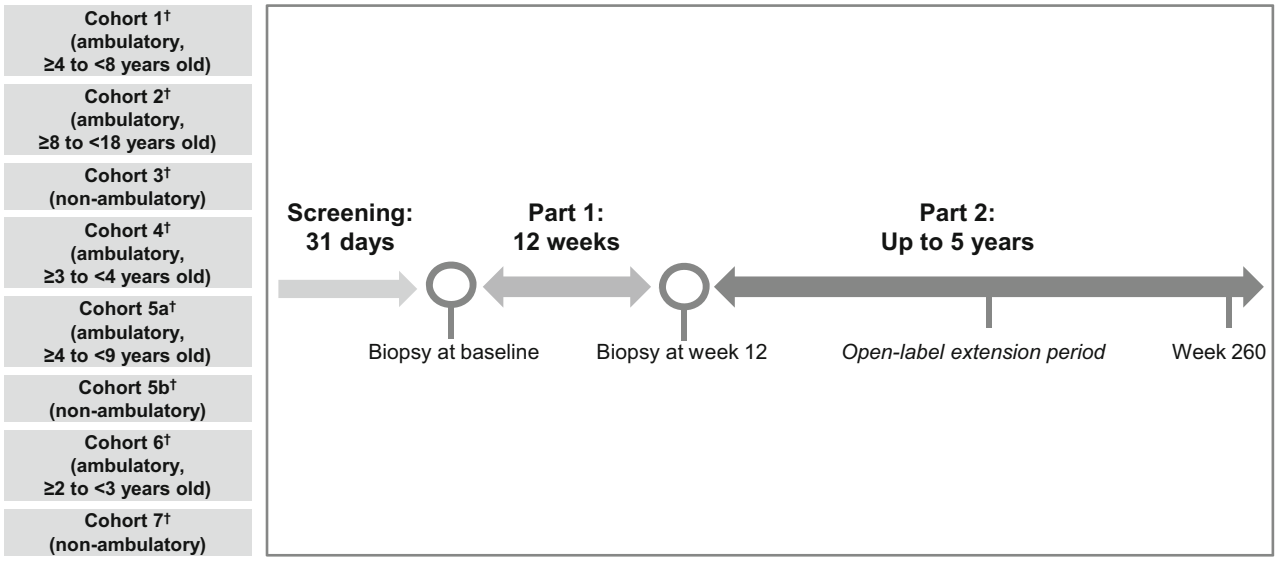


FIGURE 1: Study design: Single intravenous infusion of commercial process delandistrogene moxeparvovec material (1.33×10^{14} vg/kg*). Cohorts 1 to 4, 6, and 7 included patients with mutations in the *DMD* gene between exons 18 and 79. Cohort 5 included patients with mutations in exons 1 to 17 but excluded those with mutations inclusive of exons 9 to 13. *Linear quantitative polymerase chain reaction. †One-year data for cohort 1 only are presented in this manuscript; 1-year data for the other cohorts are not yet available. DMD = Duchenne muscular dystrophy.

criteria were: left ventricular ejection fraction <40% by echocardiogram or clinical signs and/or symptoms of cardiomyopathy; presence of any significant genetic disease other than DMD; diagnosis of an autoimmune disease; concomitant illness or requirement for chronic drug treatment that, in the opinion of the investigator, creates unnecessary risks for gene transfer; and cognitive delay or impairment that could, in the opinion of the investigator, confound motor development.

During screening and baseline visits, patient medical history, demographics, documentation of DMD genotyping, vital signs, and biologic samples (eg, blood, saliva, urine, and feces) were collected, and various clinical assessments were performed. One day prior to gene transfer, patients began receiving daily prednisone or prednisolone (1 mg/kg) in addition to their continued baseline corticosteroid dose, for a total ≤60 mg/day, which was continued for ≥60 days post-treatment and subsequently tapered, depending on serum γ-glutamyl transferase levels.

Nonclinical studies determined that 1.33×10^{14} vg/kg of delandistrogene moxeparvovec by linear quantitative polymerase chain reaction (qPCR; equivalent to 2.0×10^{14} vg/kg by supercoiled qPCR) is the effective dose based on functional improvement (specific force in the tibialis anterior and diaphragm muscle) and histological improvement (central nucleation, normalization of fiber size, decreased fibrosis).[28] Patients received a single intravenous dose of 1.33×10^{14} vg/kg of delandistrogene moxeparvovec (titrated using linear qPCR) on day 1. There was a two-part follow-up period. Part 1 comprised day= 1 post-infusion through week 12; part 2 began 12 weeks post-treatment, with functional outcomes assessed at various time points, including 1 year, and continued monitoring through 260 weeks (5 years).

Endpoints

The primary endpoint was the change in quantity of delandistrogene moxeparvovec micro-dystrophin from baseline to week 12, as measured by western blot. Secondary endpoints included: (1) vector shedding in the saliva, urine, and feces, assessed by droplet digital polymerase chain reaction (ddPCR); (2) safety, assessed by the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), or clinically significant abnormalities in laboratory or vital signs; (3) change in delandistrogene moxeparvovec micro-dystrophin expression from baseline to week 12, as measured by muscle fiber immunofluorescence intensity and percent dystrophin-positive fibers (PDPF). Exploratory endpoints included: vector genome copies in skeletal muscle biopsies, assessed by ddPCR; and impact on motor function, assessed by the NSAA and timed function tests (time to rise from the floor [supine to stand], time to ascend 4 steps, 100MWR, and 10-meter Walk/Run [10MWR]).

Sample Collection

Biopsies from the medial gastrocnemius, or alternatively allowed muscle groups, were collected using open or VACORA core biopsies in accordance with allocation protocols. Baseline and week 12 biopsies were taken from contralateral legs. Biopsy samples, collected at study sites, were mounted, frozen in isopentane, and transferred to the sponsor laboratory, where they were stored in liquid nitrogen. Saliva, urine, and feces (fecal swabs) samples were collected at pre-specified time points post-treatment for evaluation of vector shedding. The collected samples were stored in appropriate conditions to minimize degradation of nucleic acids.

Western Blot Analysis of Delandistrogene Moxeparvovec Micro-Dystrophin

Western blots were performed under Good Clinical Laboratory Practice standards, according to validated methodology adapted from Charleston et al.[29] Briefly, biopsied samples were homogenized and total protein was assayed. A total of 20 μg total protein per sample were loaded along with negative controls and a 5-point standard curve (recombinant micro-dystrophin [Curia, Albany, NY, USA] ranging from 21.85 to 349.58 fmol/mg protein) in sodium dodecyl-sulfate polyacrylamide gel electrophoresis (Invitrogen, Waltham, MA, USA). Membranes with transferred proteins were probed with DYS3 primary antibody (1:20; Leica Biosystems, Wetzlar, Germany), followed by anti-mouse immunoglobulin G-conjugated horseradish peroxidase (1:1,000; GE Healthcare, Chicago, IL, USA). The bound enzyme activity was visualized with a chemiluminescence imaging system (Alliance Q9 Advanced Imager; UVITEC, Cambridge, UK) and the bands were analyzed using Image Quant TL Plus software (GE Healthcare). To quantify delandistrogene moxeparvovec micro-dystrophin in each sample, data were normalized to each patient's muscle content. Control samples used in the assay validation were kindly provided by Dr Steven A. Moore, Wellstone Center, University of Iowa, City of Iowa, IA, USA.

Immunofluorescence Analysis of Delandistrogene Moxeparvovec Micro-Dystrophin

Briefly, delandistrogene moxeparvovec micro-dystrophin expression was analyzed by indirect immunofluorescence staining using the following antibodies: anti-dystrophin (DYS3; Leica Biosystems) at 1.4 μg/mL for 60 minutes and anti-laminin 2 alpha (Abcam, Cambridge, UK) at

5.5 μg/mL for 60 minutes. The appropriate secondary antibody cocktail (Thermo Scientific, Waltham, MA, USA) was used at 5 μg/mL for 30 minutes to detect dystrophin (Alexa Fluor 594) and laminin 2 alpha (Alexa Fluor 488). All slides were then scanned on a 3DHISTECH Pannoramic MIDI fluorescent scanner (PerkinElmer, Waltham, MA, USA) at a fixed exposure time. Using Flagship Biosciences (Morrisville, NC, USA) proprietary software, scanned images were marked for regions of inclusion and exclusion (tissue folds, staining artifacts, etc.). Next, a machine learning algorithm was applied to identify each muscle fiber based on laminin 2 alpha immunofluorescence staining, and the dystrophin localized on each muscle fiber membrane was quantified. Sections from a non-dystrophic muscle biopsy were included in each staining batch as normal controls. All activities were overseen by a pathologist.

Vector Genome Quantification

Delandistrogene moxeparvovec vector genome copies, utilizing a primer probe set targeting the MHCK7 promoter, were quantified in muscle biopsies at baseline and 12 weeks post-treatment by ddPCR. The results of the analysis were reported as vector genome copies per nucleus.

Safety Assessments

Safety was assessed by the incidence of TEAEs and SAEs, or clinically significant abnormalities in laboratory or vital signs. Additionally, electrocardiograms and echocardiograms were monitored for clinically significant abnormalities.

Vector Shedding

The kinetics of post-treatment vector shedding were approximated by the quantification of vector genome copies in saliva, urine, and feces by ddPCR, until 3 consecutive results were below the level of detection. The limits of detection of vector genome copies for urine, saliva, and feces were 5E2 vector genome copies/mL, 2.5E3 vector genome copies/mL, and 2E2 vector genome copies/μg, respectively. This method used primer probes specific to the MHCK7 promoter (within the SRP-9001 dystrophin gene cassette).

Functional Assessments

Muscle function was assessed with the NSAA, a 17-item, validated functional rating scale, specifically developed for measuring motor function in ambulatory patients with DMD.[30] Each item on the NSAA was scored between 0 and 2, with a maximum total score of 34, where: 0 = unable to perform independently; 1 = able to perform with assistance; and 2 = normal, able to perform without assistance. Other functional outcomes assessed included timed function tests: supine to stand, time to ascend 4 steps, 100MWR, and 10MWR. Functional assessments were conducted by physiotherapists at each of the study sites. Every effort was made to have each patient sequentially assessed by the same clinical evaluator, and at the same time of day.

Statistical Analysis

Data analyses were primarily descriptive in nature. For continuous variables, means, medians, standard deviations (SDs), and ranges were calculated. For categorical variables, frequency counts and percentages were calculated. For biologic endpoints, within-group change from baseline to week 12 was assessed using a permutation test, with 10,000 permutations. The permutation test was based on a 1-sample t test statistic to compare the post-treatment assessment at week 12 with the pre-treatment assessment.

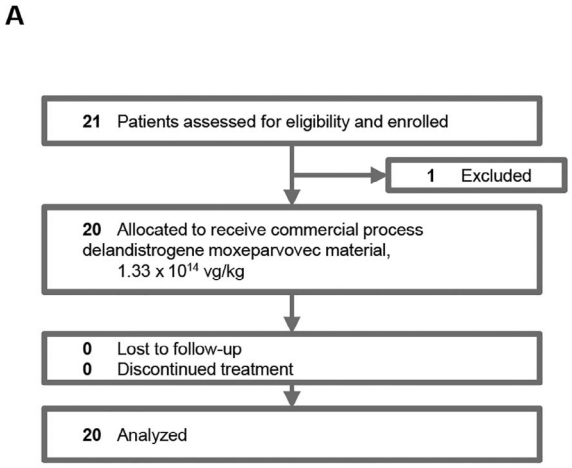
External Natural History Control Cohort and Propensity Score Weighting

A rigorous, well-matched, propensity score-weighted external natural history control (ENHC) cohort was developed as a pre-specified analysis for comparison with cohort 1, prior to interim data extraction. The ENHC cohort was derived from the following studies: Cooperative International Neuromuscular Research Group DMD Natural History Study (CINRG/DNHS[31,32]; NCT00468832),[33] a prospective natural history study; the Finding the Optimum Regimen for DMD (FOR-DMD[34]; NCT01603407)[35] study, a double-blind study comparing three widely used corticosteroid regimens (only patients on the daily regimen were included); and the Lilly Tadalafil Study (H6D-MC-LVJJ; NCT01865084),[36] a phase 3, placebo-controlled study (only patients from the placebo arm were utilized for the EC).

The following entry criteria were used to ensure that the ENHC cohort was consistent with cohort 1: aged ≥4 to <8 years; NSAA total score ≥13 and ≤30; supine to stand ≤10.4 seconds; 10MWR ≤9.1 seconds; and on a stable dose or dose equivalent of oral corticosteroids for ≥12 weeks, pre-baseline. These criteria resulted in an ENHC cohort of N = 108 (CINRG/DNHS, n = 15; FOR-DMD, n = 78; Lilly Tadalafil Study, n = 15). Propensity scores for both cohort 1 and the ENHC cohort were estimated by logistic regression analyses, based on key prognostic factors in DMD, including age group, baseline NSAA total score, and key timed function tests (supine to stand and 10MWR). After excluding 17 patients with propensity scores outside of the range for cohort 1, the ENHC cohort consisted of 91 patients. The propensity score-weighted ENHC population included all

patients with overlapping propensity scores, to avoid potential selection biases associated with 1:1 propensity-score matching.

A weighted linear regression model was developed using the covariates of the treatment group: baseline age group, baseline NSAA total score, and baseline age group



B

Characteristic	Cohort 1 (n = 20) Mean (SD) Min–max
Age, years	5.8 (1.1) 4.4–7.9
Height, cm	108.8 (7.7) 94.4–121.0
Dosing weight, kg	21.2 (4.2) 15.2–33.1
BMI, kg/m^2	17.8 (2.3) 15.0–24.6
Years since corticosteroid treatment started	1.0 (0.9) 0.1–4.1
Years since DMD diagnosis	2.4 (1.4) 0.9–6.7
NSAA total score	22.1 (3.0) 18.0–26.0
100MWR, seconds	64.1 (20.7) 42.7–119.8
Time to ascend 4 steps, seconds	3.6 (1.0) 1.9–5.5
Supine to stand, seconds	4.2 (1.4) 2.4–8.2
10MWR, seconds	5.1 (0.8) 3.5–6.7

FIGURE 2: Patient disposition and baseline clinical characteristics of cohort 1. 10MWR = 10-meter Walk/Run; 100MWR = 100-meter Walk/Run; BMI = body mass index; DMD = Duchenne muscular dystrophy; NSAA = North Star Ambulatory Assessment; SD = standard deviation.

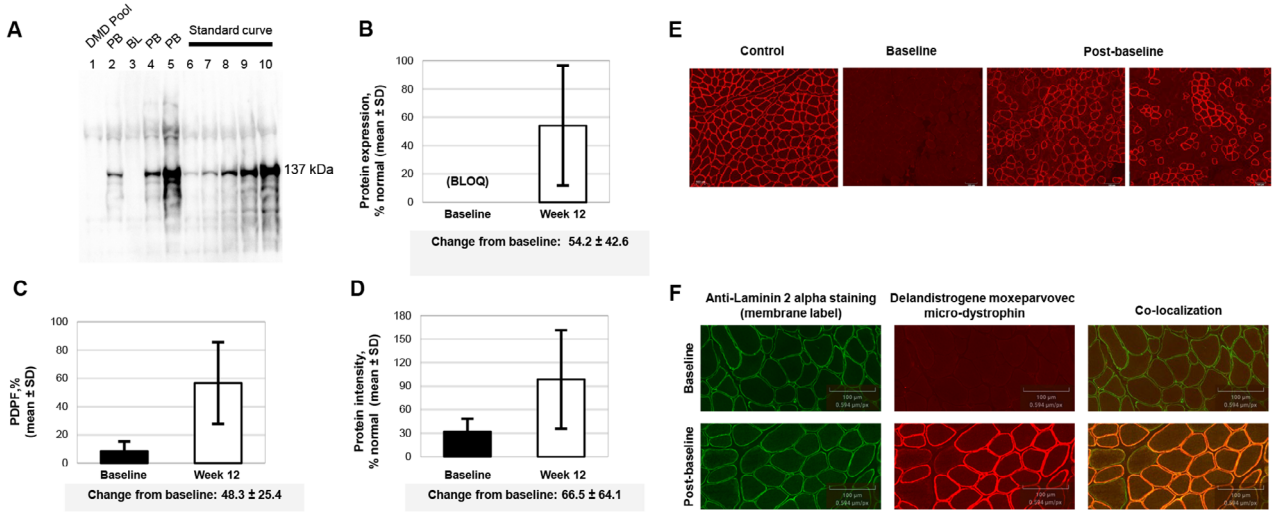
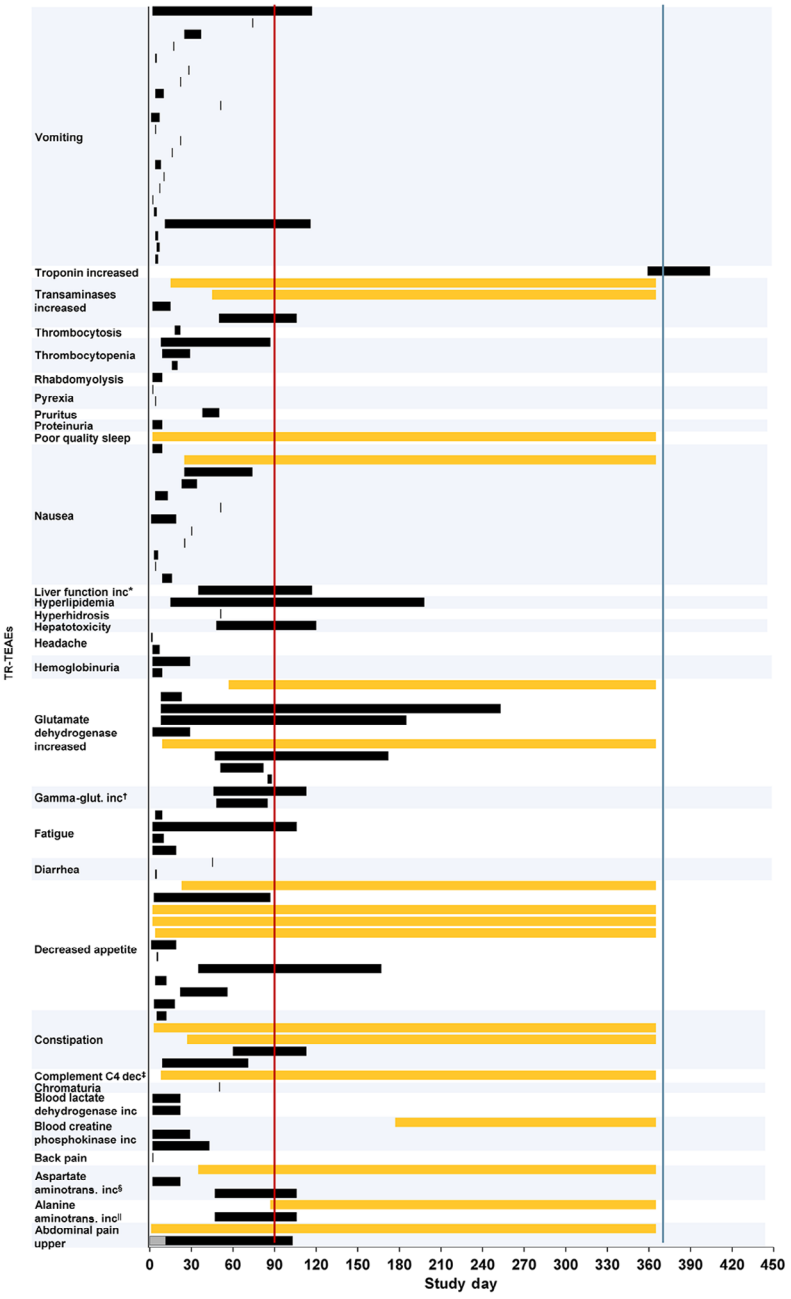


FIGURE 3: Delandistrogene moxeparvovec micro-dystrophin expression and sarcolemmal localization at 12 weeks post-infusion in cohort 1. Quantification of mean (A) western blot for delandistrogene moxeparvovec micro-dystrophin. Lanes 1 to 5 indicate: DMD pool (negative control), PB, BL, PB, PB; lanes 6 to 10 indicate: recombinant micro-dystrophin standard curve (21.85, 43.70, 87.39, 174.79, 349.58 fmol/mg). The 137 kDa line denotes the presence of delandistrogene moxeparvovec micro-dystrophin, (B) percentage of normal protein expression, as measured by western blot (BLOQ for western blot is <3.42% of normal control or 21.85 fmol/mg), (C) PDPF, as measured by IF, (D) percentage of normal protein intensity at the sarcolemma, as measured by IF, (E) representative IF images of biopsied sections of gastrocnemius muscle stained with dystrophin antibody. Left to right: normal expression in control tissue, pre-treatment baseline expression, and select images of week 12 post-baseline expression, (F) delandistrogene moxeparvovec micro-dystrophin expression at week 12 post-infusion. Example images, based on biopsies of gastrocnemius muscle in cohort 1*. Laminin 2 alpha (green) is an extracellular matrix protein that connects to dystrophin at the sarcolemma through interactions with dystroglycans and sarcoglycans in the dystrophin-associated protein complex. Thus, co-localization of delandistrogene moxeparvovec micro-dystrophin (red) with laminin 2 alpha (green) demonstrates correct sarcolemmal localization. *N = 20 patients in cohort 1; images are representative of a participant with 98% PDPF following treatment with delandistrogene moxeparvovec. BL = baseline; BLOQ = below limit of quantification; DMD = Duchenne muscular dystrophy; IF = immunofluorescence; PB = post-baseline; PDPF = percent dystrophin-positive fibers; SD = standard deviation.

by baseline NSAA total score interaction. The average treatment effect on the treated weight was used for each patient: cohort 1 patients were given a weight of 1 and the weights for ENHC patients were calculated as (propensity score) / (1-propensity score). The estimated treatment effect, 95% CI, and *p*-value were presented for the between-group comparison.

Approvals, Guidelines, and Informed Consent

ENDEAVOR was approved by a central institutional review board through Advarra. Informed consent was obtained from all legal guardians of minor participants prior to performing any procedures required for this study in compliance with all applicable guidelines.[37] Transparent Reporting of Evaluations with Nonrandomized



TR-TEAEs, n (%)	Mild n = 90	Moderate n = 12	Severe n = 3
Vomiting	19 (21.1)	2 (16.7)	1 (33.3)
Troponin increased	1 (1.1)	0	0
Transaminases increased	3 (3.3)	0	1 (33.3)
Thrombocytosis	0	1 (8.3)	0
Thrombocytopenia	2 (2.2)	1 (8.3)	0
Rhabdomyolysis	0	1 (8.3)	0
Pyrexia	2 (2.2)	0	0
Pruritus	1 (1.1)	0	0
Proteinuria	1 (1.1)	0	0
Poor quality sleep	1 (1.1)	0	0
Nausea	10 (11.1)	2 (16.7)	0
Liver function test increased	0	1 (8.3)	0
Hyperlipidemia	1 (1.1)	0	0
Hyperhidrosis	1 (1.1)	0	0
Hepatotoxicity	0	1 (8.3)	0
Headache	2 (2.2)	0	0
Hemoglobinuria	2 (2.2)	0	0
Glutamate dehydrogenase increased	8 (8.9)	1 (8.3)	0
Gamma-glutamyltransferase increased	0	1 (8.3)	1 (33.3)
Fatigue	4 (4.4)	0	0
Diarrhea	2 (2.2)	0	0
Decreased appetite	10 (11.1)	1 (8.3)	0
Constipation	5 (5.6)	0	0
Complement factor C4 decreased	1 (1.1)	0	0
Chromaturia	1 (1.1)	0	0
Blood lactate dehydrogenase increased	2 (2.2)	0	0
Blood creatine phosphokinase increased	3 (3.3)	0	0
Back pain	1 (1.1)	0	0
Aspartate aminotransferase increased	3 (3.3)	0	0
Alanine aminotransferase increased	2 (2.2)	0	0
Abdominal pain upper	2 (2.2)	0	0

FIGURE 4: Timing of treatment-related treatment-emergent adverse events (TR-TEAEs) in cohort 1 of ENDEAVOR. Each bar represents a single TR-TEAE in an individual patient. Black bars indicate time of onset and resolution of resolved TR-TEAEs as of the data cut-off (84% [88/105]). Yellow bars indicate time of onset of ongoing TR-TEAEs as of the data cut-off. The vertical red line indicates 90 days post-treatment. The gray bar indicates an unknown start date of an instance of upper abdominal pain. *Liver function test increased. †Gamma-glutamyl transferase increased. ‡Complement factor C4 decreased. §Aspartate aminotransferase increased. ||Alanine aminotransferase increased. Inc. = increased.

Designs guidelines were followed in the development of this manuscript.[38]

Results

Baseline Clinical Characteristics of Cohort 1

A total of 21 male patients with a genotype-confirmed diagnosis of DMD were screened for entry, with one screen failure, resulting in 20 patients enrolled in the study. Patients received a single intravenous infusion of delandistrogene moxeparvovec (1.33×10^{14} vg/kg;). Mean (SD) age at enrollment was 5.8 (1.1) years, and mean (SD) baseline pre-treatment NSAA total score was 22.1 (3.0). Baseline characteristics for cohort 1 are shown in Fig 2B.

Delandistrogene Moxeparvovec Micro-Dystrophin Expression and Sarcolemmal Localization

The number of vector genome copies per nucleus was assessed in muscle tissue to confirm successful transduction of target cells. The mean change from baseline (SD) to week 12 in vector genome copies per nucleus was 3.4 (2.4). Correspondingly, a change from baseline to week 12 was also observed in delandistrogene moxeparvovec micro-dystrophin by western blot and immunofluorescence analyses. Western blot revealed a mean (SD) change in micro-dystrophin expression from baseline to week 12 of 54.2% (42.6) of normal control protein (Fig 3A,B). Furthermore, expression of this micro-dystrophin following treatment with delandistrogene moxeparvovec and, importantly, its correct sarcolemmal localization, was confirmed by immunofluorescence analysis (Fig 3E), which showed a mean (SD) increase in the percentages of normal PDPF and fiber intensity, from baseline to week 12, of 48.3% (25.4) and 66.5% (64.1), respectively (Fig 3C,D). Selected example images from biopsies of the gastrocnemius muscle demonstrated co-localization of delandistrogene moxeparvovec micro-dystrophin with laminin 2 alpha, an extracellular matrix protein that connects to dystrophin at the sarcolemma through interactions with dystroglycans and sarcoglycans in the dystrophin-associated protein complex[39] (Fig 3F).

Cohort 1 Safety

There were a total of 181 adverse events (AEs) reported; 177 of these were TEAEs, of which 105 were treatment-related TEAEs (TR-TEAEs). A total of 18 patients (90%) experienced 105 TR-TEAEs, 84% (88/105) of which resolved (Fig 4). Nearly all the TR-TEAEs began within the first 90 days of infusion. Most patients (83% [15/18]) experienced TR-TEAEs that were mild to moderate in severity, and nearly all TR-TEAEs occurred within the

Table. Cohort 1 safety summary

Safety summary	Cohort 1 N = 20
Total number of AEs, n	181
Patients with at least one AE, n (%)	19 (95.0)
Total number of TEAEs, n	177
Patients with at least one TEAE, n (%)	19 (95.0)
Total number of TR-TEAEs, n	105
Patients with at least one TR-TEAE, n (%)	18 (90.0)
Total number of SAEs, n	2
Patients with at least one SAE, n (%)	2 (10.0)
Treatment-related SAE, n (%)	2 (10.0)
Patients with an AE leading to study discontinuation, n	0
Deaths, n	0
SAEs by preferred term, number of patients (% of total cohort)	
Increased transaminases	1 (5.0)
Vomiting	1 (5.0)
TR-TEAE by preferred term, number of patients (% of total cohort)	
Vomiting	11 (55.0)
Decreased appetite	9 (45.0)
Glutamate dehydrogenase increased	8 (40.0)
Nausea	8 (40.0)
Constipation	5 (25.0)
Fatigue	4 (20.0)
Transaminases increased	4 (20.0)
Aspartate aminotransferase increased	3 (15.0)
Blood creatine phosphokinase increased	3 (15.0)
Thrombocytopenia	3 (15.0)
Abdominal pain upper	2 (10.0)
Alanine aminotransferase increased	2 (10.0)
Blood lactate dehydrogenase increased	2 (10.0)
Headache	2 (10.0)
Hemoglobinuria	2 (10.0)
Gamma-glutamyl transferase increased	2 (10.0)
Pyrexia	2 (10.0)
Diarrhea	1 (5.0)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TR-TEAE = treatment-related treatment-emergent adverse event.

A Mean vector genome DNA at peak compared with week 4

Sample	Mean peak concentration (vgc/mL)	Mean week 4 concentration (vgc/mL)	Percentage decrease from peak to week 4
Saliva	5.6×10^7 (n = 15; Day 1)	1.4×10^4 (n = 12)	99.97%
Urine	4.8×10^5 (n = 17; Day 1)	1.7×10^3 (n = 18)	99.64%
Feces	2.4×10^7 (n = 13; Week 2)	1.1×10^4 (n = 11)	99.99%

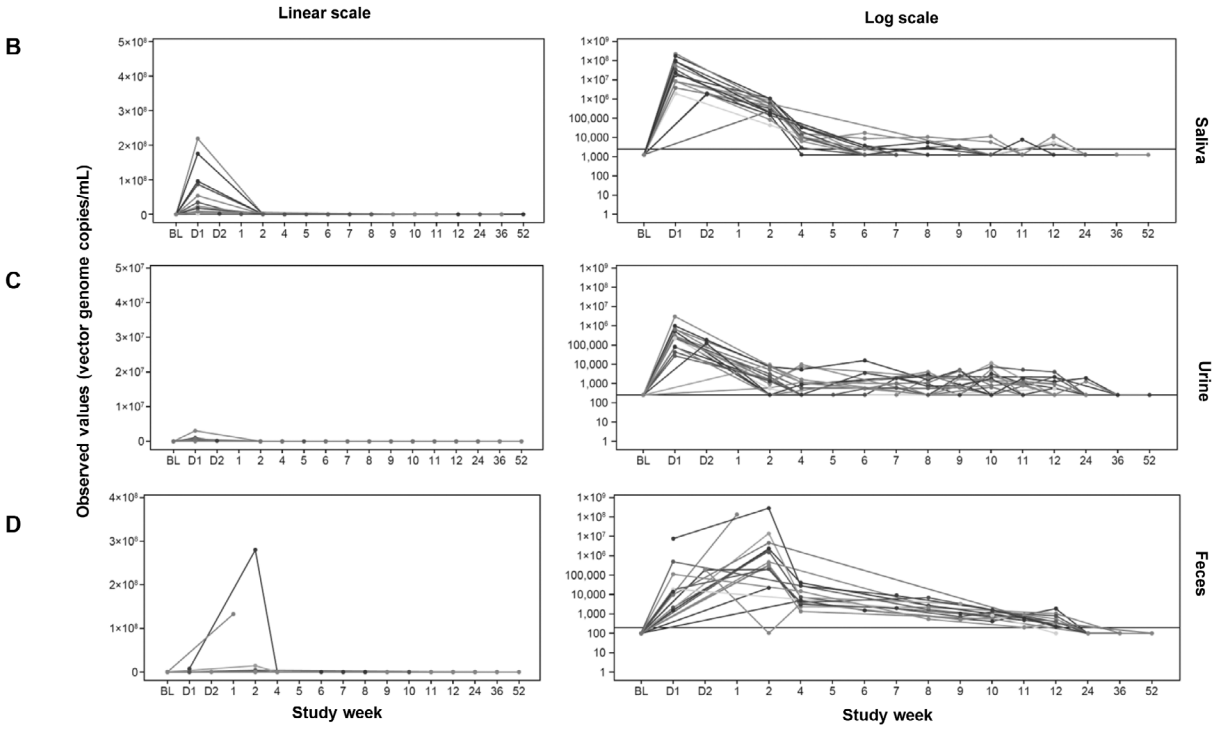


FIGURE 5: Vector shedding. (A) Mean vector genome DNA measurements at peak (peak at day 1 in saliva and urine; peak at week 2 in feces) compared with week 4. Quantification of delandistrogene moxeparvovec vector shedding over time (linear and log scales) for cohort 1 of the ENDEAVOR study population for (B) saliva, (C) urine, and (D) feces. BL = baseline; D = day; vgc = vector genome copies.

first 90 days of infusion. Vomiting was the most common TR-TEAE, occurring in 55% (11/20) of patients. Two patients experienced two treatment-related SAEs. One patient, aged 7 years, experienced an increase in liver enzymes approximately 7 weeks after infusion with delandistrogene moxeparvovec that was deemed clinically significant and required hospitalization. There were no signs or symptoms of liver dysfunction, and bilirubin and international normalized ratio remained normal. The patient responded to intravenous corticosteroids and the event was considered resolved after approximately 2 months. A hepatologist assessed the clinical course, including laboratory data, as being compatible with an adaptive immune attack on the liver due to viral capsid degradation and presentation by hepatocytes. A second SAE was vomiting that required intravenous hydration. Creatine kinase levels were relatively stable over the course of 1 year (mean [SD] change from baseline to year 1: −1,398.71 [7,280.78] U/L). Complement levels were monitored and no related clinical events were observed. There were no AEs leading to study discontinuation or deaths. A full summary of AEs reported in cohort 1 is listed in Table.

Vector Shedding

The magnitude of vector shedding and rate of clearance following administration of delandistrogene moxeparvovec were evaluated indirectly through the quantification of vector genome in samples from urine, saliva, and feces by ddPCR. Vector shedding peaked at roughly day 1 in saliva and urine, and at week 2 in feces. The mean concentration in all samples declined significantly by week 4, where the percentage decrease from peak to week 4 was >99% (Fig 5).

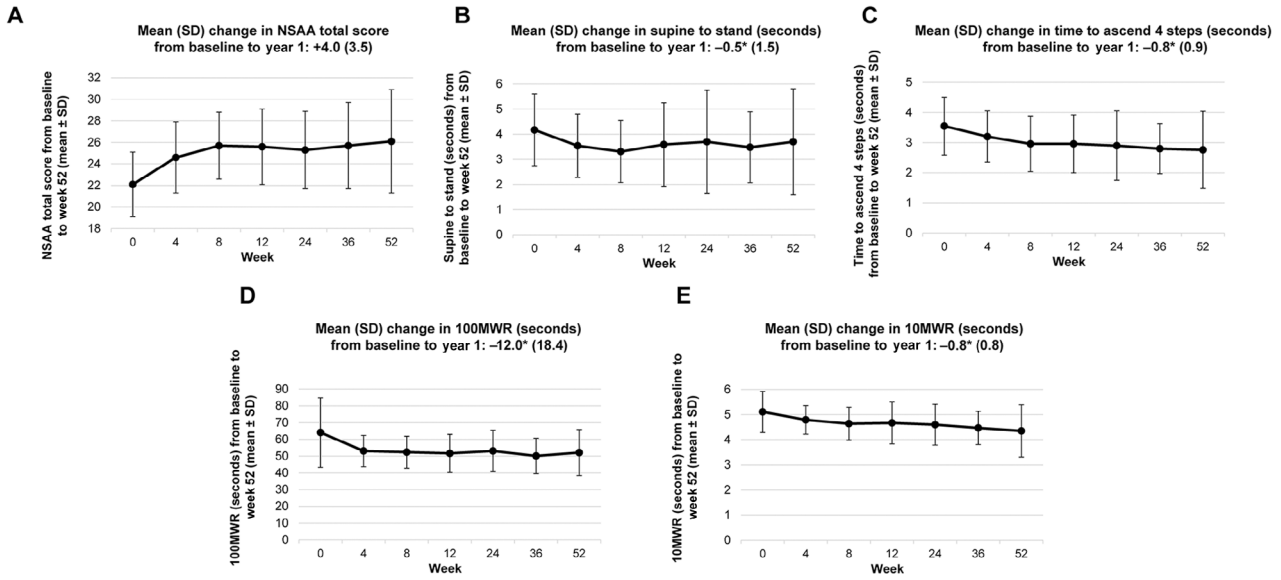


FIGURE 6: Functional assessments in cohort 1. North Star Ambulatory Assessment (NSAA) total scores and timed function tests, 1 year post-infusion with delandistrogene moxeparvovec Quantification of mean change from baseline to year 1 in (A) NSAA total score, (B) supine to stand, (C) time to ascend 4 steps, (D) 100-meter Walk/Run (100MWR), and (E) 10-meter Walk/Run (10MWR). *Negative values show an improvement in the time taken to achieve this endpoint. SD = standard deviation.

A

Baseline characteristic	ENDEAVOR cohort 1 (N = 20)	ENHC cohort (N = 91)*
Age, years (mean SD)	5.8 (1.1)	6.2 (0.4)
Min–max	4.4–7.9	4.2–7.9
NSAA total score (mean SD)	22.1 (3.0)	21.9 (1.9)
Min–max	18.0–26.0	13.0–30.0
Supine to stand, seconds (mean SD)	4.2 (1.4)	4.2 (0.6)
Min–max	2.4–8.2	1.9–9.9
Time of 10MWR, seconds (mean SD)	5.1 (0.8)	5.1 (0.4)
Min–max	3.5–6.7	3.0–7.5

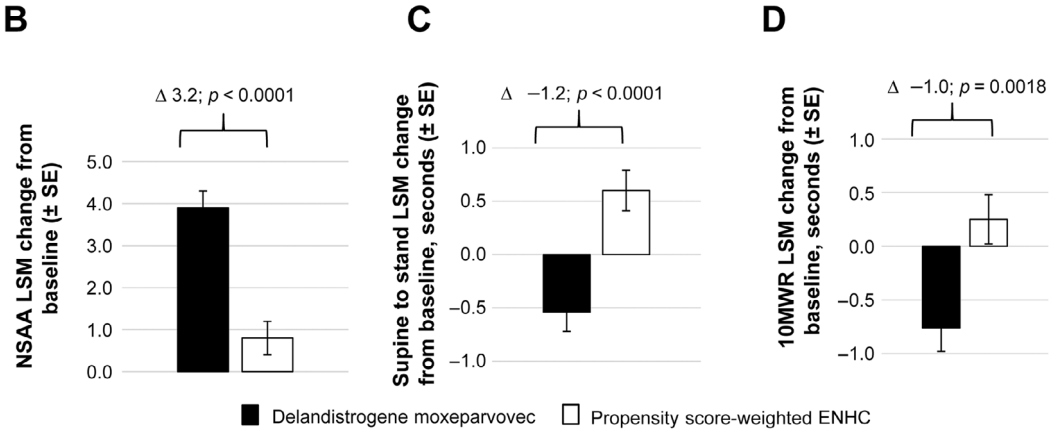


FIGURE 7: ENDEAVOR cohort 1 compared with a propensity score-weighted external natural history control (ENHC) cohort: Functional outcomes (North Star Ambulatory Assessment [NSAA] and timed function tests) at baseline and at year 1. (A) The table lists baseline characteristics for cohort 1 of ENDEAVOR and the ENHC cohort. A well-matched propensity score-weighted ENHC cohort was used to contextualize the ENDEAVOR cohort 1 functional outcomes. Statistically significant differences were observed between ENDEAVOR cohort 1 and the ENHC cohort at 1 year post-infusion in (B) NSAA total score, (C) supine to stand, and (D) 10-meter Walk/Run (10MWR). Comparisons with ENHC data are not available for 10-meter Walk/Run (100MWR) and time to ascend 4 steps. *N = 108 before propensity-score weighting. After excluding patients with non-overlapping propensity scores, N = 91. LSM = least squares mean; SD = standard deviation; SE = standard error.

Functional Outcomes

The mean (SD) NSAA total score in patients treated with delandistrogene moxeparvovec was 22.1 (3.0) at baseline and 26.1 (4.8) at year 1, with a difference of +4.0 (3.5; Fig 6A). Timed function tests (supine to stand, time to ascend 4 steps, 100MWR, and 10MWR) also showed improvement from baseline to 1 year post-treatment, with patients able to complete all the functional assessments more quickly following administration of delandistrogene moxeparvovec (Fig 6B–E).

To contextualize the functional outcomes, a propensity score-weighted ENHC cohort was utilized. Baseline clinical characteristics of cohort 1 (N = 20) versus the ENHC cohort (N = 91) are shown in the table in Fig 7A. Patients treated with delandistrogene moxeparvovec demonstrated a statistically significant improvement in 1-year NSAA compared with the ENHC cohort (least squares mean [change from baseline ± standard error]: 3.9 ± 0.4 vs 0.8 ± 0.4; Δ3.2; $p < 0.0001$; Fig 7B). From baseline to year 1, patients treated with delandistrogene moxeparvovec were also faster on timed function tests: supine to stand, least squares mean of −1.2 seconds ($P < 0.0001$; Fig 7C) and 10MWR, least squares mean of −1.0 seconds ($p = 0.0018$; Fig 7D), relative to the ENHC cohort. Comparisons with ENHC data are not available for the 100MWR and time to ascend 4 steps.

Discussion

ENDEAVOR is the first clinical study using commercial process delandistrogene moxeparvovec. The commercial process material was designed to enable large-scale production under good manufacturing practice conditions for concentration, purity, biosafety, and potency within pre-defined windows for a drug lot to be released, thus ensuring quality and consistency. The safety and efficacy profile of the commercial process material in ENDEAVOR cohort 1 was consistent with what has been observed with the clinical process material, used in SRP-9001-101[10,40] and SRP-9001-102.[41] Most TR-TEAEs were mild to moderate in severity. A total of 84% of TR-TEAEs resolved; there were no new safety signals identified in cohort 1 and none associated with clinically relevant complement activation. Although not reported in this manuscript, there were two new treatment-related SAEs in cohort 2 of the ongoing ENDEAVOR study: (1) immune-mediated myositis in a single 9-year-old male with a large deletion mutation spanning exons 3 to 43; and (2) myocarditis, with maintenance of normal cardiac function, in a single 11-year-old male initially hospitalized for nausea and vomiting.[42] Due to an emerging concern regarding immune-mediated myositis arising from immune responses to the transgene product, the protocol was amended to exclude patients with mutations within exons 1 to 17. Cohort 5 of ENDEAVOR (Study SRP-9001-103) will still permit dosing of patients with mutations in exons 1 to 17, to identify potentially immunogenic epitopes within this domain. Additional safety monitoring will be implemented for this cohort.

In a rat model of DMD exhibiting cardiac dysfunction, there was no evidence of cardiac toxicity at 12 and 24 weeks post-treatment with delandistrogene moxeparvovec at a clinical dose of 1.33×10^{14} vg/kg. However, there were improvements in echocardiogram parameters and ambulation.[43] Additionally, transduction, expression, and correct localization of delandistrogene moxeparvovec micro-dystrophin in the DMD rat model were found to be consistent with findings in the DMD mouse model, as well as in a nonhuman primate model (manuscript in review). These results, taken together with longer-term follow-up from studies 101 and 102, demonstrate the myocardial safety of delandistrogene moxeparvovec; nevertheless, extended follow-up and assessments are warranted to ensure the durability of treatment and long-term safety. Results from biodistribution and vector shedding data from ENDEAVOR cohort 1 were consistent with published data from other AAV-based gene therapy products, currently approved or in development.[44,45] Compared with the dose of delandistrogene moxeparvovec (1.33×10^{14} vg/kg), the amount of vector shed was very low, peaked in the first couple of days (saliva, urine) or weeks (feces) post-treatment, and decreased rapidly to a level below the limits of detection by week 4. Importantly, the results correspond solely to the amount of a specific sequence of the vector genome (the MHCK7 promoter), and are not indicative of an infectious virus.

ENDEAVOR cohort 1 data, collected as early as 12 weeks post-treatment, demonstrated robust transduction of target muscle, and corresponding expression and sarcolemmal localization of delandistrogene moxeparvovec micro-dystrophin that is likely to continue beyond 12 weeks at equivalent levels, as observed in SRP-9001-102.[41] In accordance with this micro-dystrophin expression, functional assessments following treatment with delandistrogene moxeparvovec showed rapid and sustained improvement over 1 year. The increases in NSAA total score observed in cohort 1 of ENDEAVOR were similar to those reported for SRP-9001-101 at year 1.[10] Notably, the improvement on NSAA observed in patients treated with delandistrogene moxeparvovec in SRP-9001-101 has been maintained for >4 years, with a mean patient age of >9 years.[40] Furthermore, in SRP-9001-102, delandistrogene moxeparvovec stabilized motor function for up to 2 years post-treatment.[41] Collectively, the delandistrogene moxeparvovec micro-dystrophin expression and functional outcomes data show that this micro-dystrophin may stabilize

the sarcolemma, thereby preserving muscle function and consequently improving the disease course in patients with DMD.

Enrollment challenges for clinical trials of rare, progressive neuromuscular diseases engender the need for use of real-world and natural history data.[46] The rarity of DMD, clinical heterogeneity of disease presentation, and variability in primary outcomes make it challenging to identify well-matched control populations large enough to provide the statistical power needed to detect clinically important treatment effects over relatively short time courses.[46,47] One way to contextualize efficacy results in the absence of a placebo arm is to use established and accepted statistical methodologies to obtain appropriately matched groups (based on baseline characteristics) from available data on untreated patients.[46,48-51] Given that all patients received treatment in this open-label study, an ENHC cohort was utilized to contextualize the functional outcomes versus what would be expected based on natural history.[31-36] This analysis showed statistically significant differences in the 1-year change in functional outcomes—NSAA total score, supine to stand, and 10MWR—for patients treated with delandistrogene moxeparvovec versus a propensity score-weighted natural history ENHC cohort, indicating that treatment with delandistrogene moxeparvovec may improve the disease course of patients with DMD. Although delandistrogene moxeparvovec is not expected to reverse damage that has already occurred, the 3.2-point improvement in NSAA compared with the ENHC cohort at 1 year is clinically meaningful and consistent with the treatment goal of stabilization of disease progression. If stabilization is maintained, this difference from the ENHC cohort is anticipated to increase over time, as observed in study SRP-9001-101. Overall, the improvement in NSAA observed is indicative of delandistrogene moxeparvovec changing the trajectory of the disease.

The limitations of this study include the small sample size of cohort 1 and the open-label nature of the study. In addition, although patients included in the ENHC cohort were treated with stable maintenance doses of corticosteroids, they did not receive the same 1 mg/kg/day for ≥60 days post-treatment increase that cohort 1 patients received. Although a pulse-increased dose of daily corticosteroids for 2 months, in addition to maintenance corticosteroids, may have transient impacts on motor performance, the effect would not be expected to persist for the 12 months of follow-up reported here. Sustained improvement for ≥4 years in functional outcomes, reported in four patients treated in SRP-9001-101, further implies that the observed improvement in motor function is not due to the 60 days of pulsed corticosteroids.[40] Although this study yielded encouraging efficacy and safety results from the first use of commercial process delandistrogene moxeparvovec material, a larger, phase 3, placebo-controlled trial to confirm these results is underway.[25]

Overall, a single administration of commercial process delandistrogene moxeparvovec material in cohort 1 of ENDEAVOR resulted in robust expression of delandistrogene moxeparvovec micro-dystrophin, an acceptable safety profile, and stabilized motor function. Collectively, these results add to the growing body of evidence suggesting a clinical benefit of delandistrogene moxeparvovec gene therapy in patients with DMD. Longer-term data from cohort 1 and results from cohorts 2 to 7 will provide further information on the safety and efficacy profile of delandistrogene moxeparvovec.

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Author Contributions

All authors contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. All authors contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

L.R.R.K. and J.R.M. are co-inventors of AAVrh74.MHCK7.SRP-9001.micro-dys technology.

Data Availability

Requests for data supporting this manuscript should be submitted to medinfo@sarepta.com.

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