Pediatric Neurology 153 (2024) 11–18

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Practical Considerations for Delandistrogene Moxeparvovec Gene Therapy in Patients With Duchenne Muscular Dystrophy

Jerry R. Mendell, MD [a, b, 1, *], Crystal Proud, MD [c], Craig M. Zaidman, MD [d], Stefanie Mason, MD [e], Eddie Darton, MD [e], Shufang Wang, PhD [e], Christoph Wandel, MD, PhD [f], Alexander P. Murphy, MD, PhD [g], Eugenio Mercuri, MD, PhD [h], Francesco Muntoni, MD [i, j], Craig M. McDonald, MD [k]

[a] *Center for Gene Therapy, The Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, Ohio*
[b] *The Ohio State University, Columbus, Ohio*
[c] *Children's Hospital of the King's Daughters, Norfolk, Virginia*
[d] *Department of Neurology, Washington University School of Medicine, St. Louis, Missouri*
[e] *Sarepta Therapeutics, Inc, Cambridge, Massachusetts*
[f] *F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[g] *Roche Products Ltd, Welwyn Garden City, United Kingdom*
[h] *Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy*
[i] *The Dubowitz Neuromuscular Centre, University College London, Great Ormond Street Institute of Child Health & Great Ormond Street Hospital, London, United Kingdom*
[j] *National Institute of Health Research, Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom*
[k] *Department of Physical Medicine & Rehabilitation, UC Davis Health, Sacramento, California*

ARTICLE INFO

Article history:
Received 19 October 2023
Accepted 2 January 2024
Available online 5 January 2024

Keywords:
Delandistrogene moxeparvovec
Duchenne muscular dystrophy
Gene therapy
Practical considerations
Safety
Adeno-associated virus (AAV)
AAVrh74

ABSTRACT

Background: Delandistrogene moxeparvovec is a gene transfer therapy approved in the United States, United Arab Emirates, and Qatar for the treatment of ambulatory patients aged four through five years with a confirmed Duchenne muscular dystrophy (DMD)-causing mutation in the *DMD* gene. This therapy was developed to address the underlying cause of DMD through targeted skeletal, respiratory, and cardiac muscle expression of delandistrogene moxeparvovec micro-dystrophin, an engineered, functional dystrophin protein.

Methods: Drawing on clinical trial experience from Study 101 (NCT03375164), Study 102 (NCT03769116), and ENDEAVOR (Study 103; NCT04626674), we outline practical considerations for delandistrogene moxeparvovec treatment.

Results: Before infusion, the following are recommended: (1) screen for anti-adeno-associated virus rhesus isolate serotype 74 total binding antibody titers <1:400; (2) assess liver function, platelet count, and troponin-I; (3) ensure patients are up to date with vaccinations and avoid vaccine coadministration with infusion; (4) administer additional corticosteroids starting one day preinfusion (for patients already on corticosteroids); and (5) postpone dosing patients with any infection or acute liver disease until event resolution. Postinfusion, the following are recommended: (1) monitor liver function weekly (three months postinfusion) and, if indicated, continue until results are unremarkable; (2) monitor troponin-I levels weekly (first month postinfusion, continuing if indicated); (3) obtain platelet counts weekly (two weeks postinfusion), continuing if indicated; and (4) maintain the corticosteroid regimen for at least 60 days postinfusion, unless earlier tapering is indicated.

Conclusions: Although the clinical safety profile of delandistrogene moxeparvovec has been consistent, monitorable, and manageable, these practical considerations may mitigate potential risks in a real-world clinical practice setting.

* Communications should be addressed to: Dr. Mendell; Sarepta Therapeutics, Inc.; 215 First Street; Cambridge, MA 02142.
E-mail address: JMendell@sarepta.com (J.R. Mendell).

[1] Employed at Nationwide Children's Hospital during this work.

https://doi.org/10.1016/j.pediatrneurol.2024.01.003

Introduction

Duchenne muscular dystrophy (DMD) is a rare, X-linked, progressive, degenerative neuromuscular disease caused by mutations in the *DMD* gene, which result in the absence of functional dystrophin protein.[1,2] Dystrophin is a large subsarcolemmal protein that plays a key structural role in muscle fibers, protecting them from damage during normal muscle contraction as part of the dystrophin-associated protein complex, which links the muscle fiber cytoskeleton to the extracellular matrix.[3-6] Irreversible muscle damage is present at birth in DMD, with increasing histologic evidence of inflammation and fibrosis in the first years of life.[7] Since the introduction of ventilatory support in most care settings in the 1990s, patients with DMD have a median life expectancy of late 20s to early 30s, with death typically resulting from respiratory and/or cardiac failure.[8-10] Thus, there is a pressing need for treatment options that can delay disease progression and improve the life expectancy of patients with DMD.

Gene therapy is a rational approach to treating monogenic neuromuscular diseases like DMD.[11] In clinical trials of gene therapies, adeno-associated virus (AAV) vectors are the most commonly used system for delivering transgenes (therapeutic genes intended to compensate for a loss of functional protein due to a disease-causing variant) to target cells/tissues.[12-14] A recombinant AAV (rAAV) is an engineered vector that traverses the membrane of target cells, where it ultimately delivers its single-stranded DNA cargo into the nucleus. Transgenes delivered to the nuclei of transduced cells by rAAVs form circular DNA molecules called episomes, which can persist long term in postmitotic cells.[15,16] These rAAV vectors can deliver therapeutic genes to a broad range of target cells and have become the vehicle of choice for *in vivo* gene transfer.[17,18] Many AAV serotypes have been described, based on their intrinsic characteristics.[19,20]

Several features make rAAV rhesus isolate serotype 74 (rAAVrh74) an attractive platform for the development of gene therapies targeting neuromuscular diseases.[21] rAAVrh74 has demonstrated widespread transgene delivery to muscles—including skeletal, respiratory, and cardiac muscles—in animal models following intravenous (IV) administration.[22-24] Moreover, because rAAVrh74 was isolated from rhesus macaques, it may be associated with less preexisting immunity compared with AAV serotypes isolated from humans.[17] One study that examined preexisting serum antibodies against a range of AAV serotypes in various populations, including patients with DMD, found rAAVrh74 to be among the serotypes with the lowest rates of preexisting immunity.[17,22] In another recently published study, samples from a cohort of 101 (of 107 enrolled) patients with DMD from across the United States were sent to a single-center laboratory and assessed for seroprevalence of total anti-AAVrh74 antibodies[21]; 13.9% of patients (age ≥4 to <18 years; mean age: 9.1 years) were seropositive.[21] Since preexisting antibodies against the AAV vector can affect the safety and efficacy of gene therapies, preventing some patients from being eligible for treatment,[25-27] the low seroprevalence of antibodies against rAAVrh74 shown in this study suggests the potential for broad applicability of rAAVrh74-based gene therapy for patients with DMD.

Delandistrogene moxeparvovec is an rAAV vector-based gene therapy approved in the United States, United Arab Emirates, and Qatar (as of September 2023) for the treatment of ambulatory patients aged four through five years with a confirmed DMD-causing mutation in the *DMD* gene, excluding patients with any deletion in exon 8 and/or exon 9.[28,29] This therapy is designed to compensate for the absence of functional dystrophin protein in DMD by delivering a transgene encoding delandistrogene moxeparvovec microdystrophin, an engineered dystrophin protein containing key functional domains of the wild-type protein.[17] This single-dose infusion uses the rAAVrh74 vector to deliver the delandistrogene moxeparvovec transgene, under the control of the MHCK7 promoter, to target skeletal, cardiac, and respiratory muscles. The gene cassette within the delandistrogene moxeparvovec rAAVrh74 vector does not encode any viral genes and is consequently incapable of replication or reversion to a replicating form. A detailed description of the rational design of delandistrogene moxeparvovec has been previously published.[17,30]

This review outlines several practical considerations to support health care professionals initiating delandistrogene moxeparvovec gene therapy in patients with DMD (Fig 1), based on clinical trial experience in 85 patients treated with delandistrogene moxeparvovec across Study 101 (SRP-9001-101; NCT03375164), Study 102 (SRP-9001-102; NCT03769116), and ENDEAVOR (Study 103; SRP-9001-103; NCT04626674). The topics span patient selection, pre- and post-treatment monitoring, adverse events (AEs) in clinical trials, and the general safety of AAV-based gene therapies.

Practical considerations of treatment with delandistrogene moxeparvovec

Evaluation of anti-AAVrh74 total binding antibodies

To ensure transduction efficiency and/or mitigate potential AEs that may arise from immune responses to the viral vector (in this case antibodies to rAAVrh74), patients must be evaluated for anti-AAVrh74 total binding antibodies (TAbs) using a TAb enzyme-linked immunosorbent assay before infusion with delandistrogene moxeparvovec. A US Food and Drug Administration (FDA)-authorized test for anti-AAVrh74 TAbs is currently not available. There is no standardized assay for measuring preexisting immunity against AAV vectors. Rather, entry into a clinical gene therapy program requires a specific antibody screening that has been validated by the sponsor, in the case of investigational drugs, or the sponsor and gene therapy manufacturer, in the case of FDA-approved products.[31,32] Importantly, program-specific assays can differ in the methodologies used for evaluating preexisting immunity. Specifically, some assays only measure antibodies that prevent AAV-mediated transduction of target host cells, known as neutralizing antibodies (NAbs); other assays measure TAbs, which, in addition to NAbs, also detect binding antibodies that do not prevent transduction, called non-NAbs.[33] Although these antibodies are not known to pose a specific risk to the efficacy of gene therapies, they can trigger the innate immune system (complement activation), which can adversely affect safety.[26] With regard to the various assay designs and evaluation of pre-existing immunity, it is also important to determine the cutoff threshold for “elevated” antibody levels, which would preclude participation in a specific gene therapy program. These thresholds are experimentally determined, through both nonclinical and clinical studies, and will be unique for each gene therapy program.

Delandistrogene moxeparvovec administration is not recommended in patients who have elevated anti-AAVrh74 total antibody titers (≥1:400, as assessed by the manufacturer-endorsed test). This total antibody threshold for seropositivity was determined through preclinical nonhuman primate studies, which found no inhibition of transduction or safety events associated with antibody titers below this threshold, and was subsequently confirmed clinically in human trials using similar assays.[17,34] Across all clinical studies, elevated anti-AAVrh74 TAb titers were observed in all patients following a one-time delandistrogene moxeparvovec infusion.[28] Thus, readministration of delandistrogene moxeparvovec is not recommended.

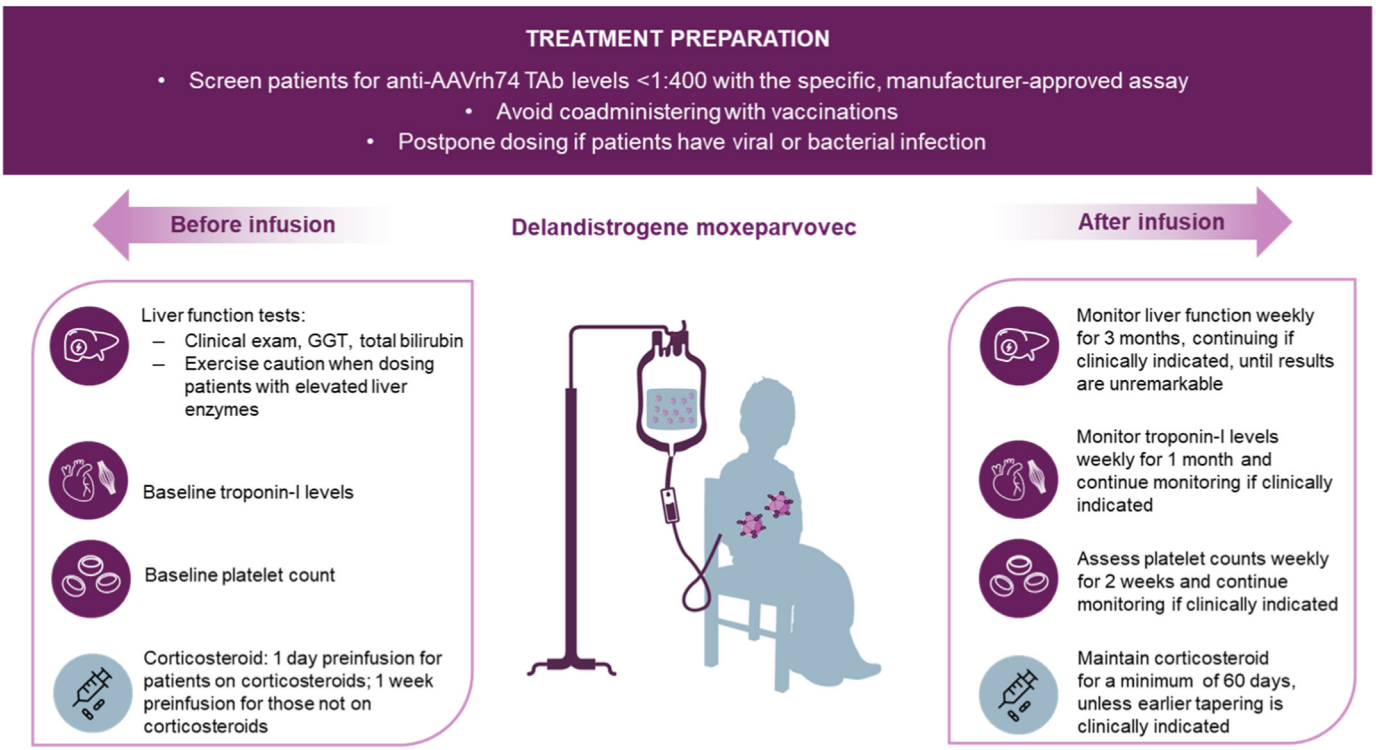

FIGURE 1. Considerations for initiating delandistrogene moxeparvovec gene transfer therapy in patients with Duchenne muscular dystrophy (DMD). AAVrh74, adeno-associated virus rhesus isolate serotype 74; GGT, gamma-glutamyl transferase; TAb, total binding antibody. The color version of this figure is available in the online edition.

Mutation-related eligibility criteria

Although identification of individuals who are seropositive for anti-AAVrh74 antibodies can help mitigate AEs associated with preexisting immunity to the vector, it does not account for individuals who may generate immune responses to the transgene product, delandistrogene moxeparvovec micro-dystrophin. Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exons 8 and/or 9 of the *DMD* gene, due to increased risk of a severe immune-mediated myositis (IMM) reaction.

Serious AEs, which involved muscle weakness with variable cardiac involvement, have occurred in at least five patients across clinical trials of AAV-based gene therapies for DMD, including delandistrogene moxeparvovec.[35-37] In the ENDEAVOR clinical trial, one patient who had a deletion spanning exons 3 to 43 of the *DMD* gene experienced a single life-threatening event of IMM, with symptoms of muscle weakness that included dysphagia, dyspnea, and hypophonia observed approximately one month following treatment. Symptoms resolved during hospitalization and following additional immunomodulatory treatment. Although the patient's muscle strength gradually improved, it did not return to preinfusion levels. The immune reaction leading to this serious AE was hypothesized to be T-cell-mediated, arising from a lack of self-tolerance to specific epitopes encoded within the N-terminal portion of the transgene.[35] In response to the event, a protocol amendment was added for existing and subsequent clinical trials to exclude patients with mutations within the N-terminal portion of the transgene, exons 1 to 17.[37] Although limited data are available concerning delandistrogene moxeparvovec treatment in patients with mutations in exons 1 to 17 and/or exons 59 to 71 of the *DMD* gene, and patients with deletions in these regions may be at risk of severe IMM, ongoing work to better characterize which mutations confer an increased risk of severe IMM following treatment with delandistrogene moxeparvovec resulted in the contraindication of deletions within exons 8 and 9.

If symptoms of myositis occur (e.g., unexplained increased muscle pain, tenderness, or weakness), additional immunomodulatory treatment (immunosuppressants [e.g., calcineurin inhibitor]) should be considered in addition to corticosteroids.

Additional pretreatment screening

It is important to establish general wellness and good health before infusion with delandistrogene moxeparvovec. During the screening period, which should begin no later than 31 days before infusion, a variety of assessments are needed—including electrocardiograms, echocardiograms, clinical laboratory assessments, urinalysis, and serology tests. Furthermore, due to an increased risk of serious systemic immune response, it is important to test for concurrent viral infections (e.g., viral hepatitis, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, parvovirus B19, varicella zoster virus, and human herpesvirus 6) and postpone treatment until any detected infection has resolved. It is also important to ensure that patients have received all vaccines recommended in current guidelines, including the seasonal influenza vaccine, before initiation of delandistrogene moxeparvovec. Coadministration of vaccines and delandistrogene moxeparvovec is not recommended. Vaccinations should be completed at least four weeks before initiating an adjusted corticosteroid regimen. In addition, before administration of delandistrogene moxeparvovec, baseline liver function (clinical examination, gamma-glutamyl transferase [GGT], and total bilirubin), platelet count, and troponin I levels should be assessed. Because the risk-benefit is not well-defined and more data are required, caution should be taken when administering AAV-based therapies to patients with unexpected elevations in liver enzymes (e.g., GGT, bilirubin) at baseline.

TABLE 1.
Preinfusion and Postinfusion Corticosteroid Dosing

Baseline Corticosteroid Dosing*	Peri-infusion Corticosteroid Dose (Prednisone Equivalent)†	Recommended Maximum Total Daily Dose (Prednisone Equivalent; Inclusive of Baseline Dose)	Recommended Corticosteroid Regimen Taper Duration
Daily or intermittent dose	Start 1 day before infusion: 1 mg/kg/day (and continue baseline dose)	60 mg/day	2 weeks (or longer, as needed) if tapering from added corticosteroids back to baseline dose
High dose for 2 days per week	Start 1 day before infusion: 1 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	60 mg/day	2 weeks (or longer, as needed) if tapering from added corticosteroids back to baseline dose
Not on corticosteroids	Start 1 week before infusion: 1.5 mg/kg/day	60 mg/day	4 weeks (or longer, as needed) if tapering from added corticosteroids back to no corticosteroids; the corticosteroids should not be stopped abruptly

* Patient continues to receive this dose.
† Deflazacort and vamorolone are not recommended for use as a peri-infusion corticosteroid.

Corticosteroid regimen

Even in the absence of preexisting antibodies (based on the threshold or lower limit of quantification), immune responses to the rAAVrh74 vector are expected following delandistrogene moxeparvovec infusion. To reduce the risk of an adverse immune response, corticosteroids should be administered before infusion, according to the schedule outlined in Table 1. No data are available on peri-infusion corticosteroids with deflazacort or vamorolone, and these agents should not be used as peri-infusion corticosteroids. Maintenance of this regimen is recommended for a minimum of 60 days postinfusion unless earlier tapering is clinically indicated. Modification of corticosteroid dose is recommended for patients with liver function abnormalities (Table 2). Caregivers should be advised to contact a health care provider immediately if a patient misses a corticosteroid dose or vomits shortly after taking a dose, which would likely reduce the dose received.

Vaccinations

During treatment with high-dose corticosteroids, patients may have a decreased ability to mount an immune response to vaccines. This could potentially impact the efficacy of vaccines and increase the risk of infection. The timing of vaccinations, both scheduled and seasonal, should be considered before administration of high-dose corticosteroids, as some vaccines may need to be adjusted or postponed. In general, live-attenuated vaccines, such as the measles, mumps, rubella, and varicella (chickenpox) vaccines, are contraindicated in patients receiving high-dose immunosuppressive therapy due to both documented and theoretical risks of disseminated infection from the vaccine virus. The live-attenuated viruses in these vaccines could potentially cause disease in patients with a weakened immune system.

Administration in patients treated with a phosphorodiamidate morpholino oligomer

Delandistrogene moxeparvovec clinical trials have required that patients should not have received any treatment designed to increase dystrophin expression (e.g., Translarna, EXONDYS 51, VYONDYS 53, VILTEPSO) within six months before infusion. This requirement was implemented to avoid confounding efficacy and safety results, which could be attributed to residual levels of the treatments mentioned above. Although this “washout” period is included in delandistrogene moxeparvovec clinical trials, based on available nonclinical data, a delay in treatment appears to not be required for the sequential use of exon-skipping therapies and delandistrogene moxeparvovec.[38]

TABLE 2.
Recommended Corticosteroid Regimen Modification for Patients With Liver Function Abnormalities Following Delandistrogene Moxeparvovec Infusion*,[28]

Peri-Infusion Corticosteroid Dosing	Modified Peri-Infusion Corticosteroid Dose (Prednisone Equivalent)†	Recommended Maximum Total Daily Dose (Prednisone Equivalent)†	Recommended Corticosteroid Regimen Taper Duration
Baseline + 1 mg/kg/day	Increase to 2 mg/kg/day (and continue baseline dose)	120 mg/day	2 weeks if tapering from added corticosteroids back to baseline dose
Baseline + 1 mg/kg/day taken on days without high-dose corticosteroid treatment	Increase to 2 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	120 mg/day	2 weeks if tapering from added corticosteroids back to baseline dose
1.5 mg/kg/day	Increase from 1.5 mg/kg/day to 2.5 mg/kg/day	120 mg/day	4 weeks if tapering from added corticosteroids back to no corticosteroids

Abbreviations:
GGT = Gamma-glutamyl transferase
IV = Intravenous
ULN = Upper limit of normal
To lower the risk of an adverse immune response, corticosteroids should be administered starting one day before delandistrogene moxeparvovec infusion if the patient is already on a corticosteroid regimen at baseline, and one week before infusion if the patient is not on corticosteroids at baseline.
* GGT ≥150 U/L and/or other clinically significant liver function abnormalities (e.g., total bilirubin >2 × ULN) following infusion. For GGT or bilirubin elevations that do not respond to these oral corticosteroid increases, IV bolus corticosteroids may be considered.
† Deflazacort is not recommended for use as a peri-infusion corticosteroid.

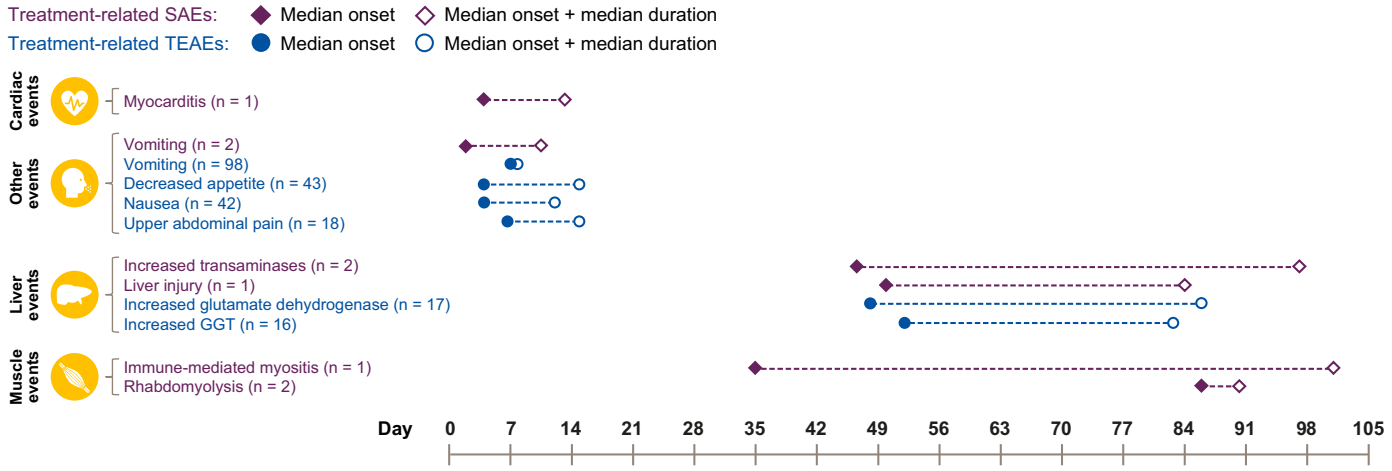

FIGURE 2. Time course of the safety profile of delandistrogene moxeparvovec (n = 85)*. *Safety assessed in 85 patients across three ongoing clinical studies: two open-label studies (Study 101[39] and ENDEAVOR)[40] and one double-blind, placebo-controlled study (Study 102).[41] As of the data cutoff dates, 45 patients from Studies 101 and 102 were treated with the clinical process delandistrogene moxeparvovec material and 40 patients from ENDEAVOR received intended commercial process delandistrogene moxeparvovec material. The overall safety profile of delandistrogene moxeparvovec in clinical trials has a predictable time course in which most TR-TEAEs occurred within 90 days post-treatment. Liver enzyme elevations began within 60 days of infusion, with an onset of ALI occurring around 51 days that lasted, on average, for eight days. TR-TEAEs listed in the figure occurred in >15% of participants. Nine TR-SAEs occurred in seven patients, including vomiting (n = 2), increased transaminases (n = 2), rhabdomyolysis (n = 2), liver injury (n = 1), IMM (n = 1), and myocarditis (identified through troponin-I monitoring; n = 1). In the case of myocarditis, MRI findings were consistent with myocarditis superimposed on preexisting DMD cardiomyopathy and resolved with sequelae. AE, adverse event; ALI, acute liver injury; DMD, Duchenne muscular dystrophy; IMM, immune-mediated myositis; MRI, magnetic resonance imaging; SAE, serious AE; TR-SAE, treatment-related serious AE; TR-TEAE, treatment-related treatment-emergent AE. The color version of this figure is available in the online edition.

Dosing and administration of delandistrogene moxeparvovec

The recommended dose of delandistrogene moxeparvovec is 1.33×10^{14} vector genomes (vg)/kg of body weight.[28] Delandistrogene moxeparvovec is infused systemically using a syringe infusion pump, with an in-line 0.2-μm adult filter, for a duration of approximately 1 to 2 hours (or longer at care team discretion) through a peripheral limb vein at a rate of less than 10 mL/kg/hour. A topical anesthetic (e.g., lidocaine 2.5%, prilocaine 2.5%, or LMX4 cream) may be applied to the skin before insertion of the IV catheter for infusion. Insertion of a backup catheter is recommended. Before the infusion, the IV catheter should be checked to confirm it is within the vein and that the IV flows well (i.e., is not interstitial).

Prevention and treatment of nausea and vomiting

Many patients in the delandistrogene moxeparvovec clinical trials have been treated with antiemetics for approximately the first week after administration, which may help ensure adequate dosing of peri-infusion corticosteroids. This medication can be continued beyond one week if nausea and/or vomiting persists or discontinued if no nausea or vomiting occurs.

Post-treatment monitoring

As with other gene therapies, it is important to closely monitor patients in the weeks and months following infusion with delandistrogene moxeparvovec. Liver function (clinical examination, GGT, and total bilirubin) should be monitored weekly for the first three months post-treatment with delandistrogene moxeparvovec, with adjustments to the corticosteroid regimen, if clinically indicated, as shown in Table 2. If acute serious liver injury is suspected, consultation with a specialist is recommended. Monitoring of liver function should continue until results are unremarkable (i.e., normalized or near baseline levels). Troponin-I levels should be monitored weekly for the first month after infusion, with continued monitoring if clinically indicated.

Platelet counts should be obtained weekly for the first two weeks, with continued monitoring if clinically indicated.

Long-term safety should be assessed by monitoring vital signs, physical examinations, electrocardiograms, echocardiograms, and selected laboratory assessments. Patients treated with delandistrogene moxeparvovec in clinical trials were monitored for safety for up to 52 weeks following treatment.

Summary of safety experience in delandistrogene moxeparvovec clinical trials

Overall, the safety profile of delandistrogene moxeparvovec in clinical trials has been monitorable and manageable, with a predictable time course (Fig 2). The safety and efficacy of delandistrogene moxeparvovec have been assessed in 85 male patients with a confirmed mutation in the *DMD* gene, across three ongoing clinical studies: Study 101 (data cutoff: October 17, 2022), Study 102 (data cutoff: October 03, 2022), and ENDEAVOR/Study 103 (data cutoff: September 19, 2022). These data are equivalent to 183 patient-years of exposure, with a mean follow-up time of 2.2 (0.5 to 4.8) years. Results are presented for all 85 patients treated with delandistrogene moxeparvovec, as well as a subset that includes 73 patients who received the FDA-recommended dose of 1.33×10^{14} vg/kg (Tables 3 and 4).

Seventy-three of 85 participants experienced a total of 366 treatment-related treatment-emergent AEs (Table 3), most of which were mild to moderate in severity and occurred within 90 days of treatment. The most common treatment-related treatment-emergent AE across all studies was vomiting (Table 4), which was reported in 58.8% of patients.

AEs of vomiting were observed as early as the day of infusion. Other common adverse reactions (incidence ≥5%), including nausea, thrombocytopenia, and pyrexia, occurred within the first two weeks following infusion. In these clinical studies, elevations in liver enzymes (aspartate aminotransferase, alanine aminotransaminase [ALT], GGT, glutamate dehydrogenase, hepatic enzymes, transaminases, blood bilirubin) were very common,

TABLE 3.
Combined AEs Across Studies of Patients Treated With Delandistrogene Moxeparvovec

Safety Results	1.33×10^{14} vg/kg (n = 73)	All* (N = 85)
Number of AEs	941	1282
Patients with any AEs, n (%)	70 (95.9)	82 (96.5)
Patients with any AEs leading to discontinuation, n (%)	0	0
Deaths, n (%)	0	0
Number of TEAEs	901	1230
Patients with any TEAEs, n (%)	70 (95.9)	82 (96.5)
Number of TR-TEAEs	328	366
Patients with any TR-TEAEs, n (%)	63 (86.3)	73 (85.9)
Number of SAEs	8	13
Patients with any SAEs, (%)	7 (9.6)	11 (12.9)
Number of TR-SAEs	6	9
Patients with any TR-SAEs, n (%)	5 (6.8)	7 (8.2)

Abbreviations:
AE = Adverse event
SAE = Serious AE
TEAE = Treatment-emergent AE
TR-SAE = Treatment-related SAE
TR-TEAE = Treatment-related TEAE
vg = Vector genomes
Summary of Study 101, Study 102, and ENDEAVOR collective safety data (N = 85) as well as safety data from patients who received the 1.33×10^{14} vg/kg dose (N = 73).
* For the integrated safety data, the clinical cutoff dates were October 17, 2022, for Study 101; April 1, 2022, for Study 102 (Part 1 only); October 3, 2022, for Study 102 (all available data); and September 19, 2022, for ENDEAVOR.

typically occurring within eight weeks following infusion. Most cases were generally asymptomatic and resolved without clinical sequelae and within 60 days, either spontaneously or following a temporary increase in systemic corticosteroids.

Although no cases of liver failure were reported, acute liver injury (ALI; defined as GGT >3 × upper limit of normal [ULN], glutamate dehydrogenase >2.5 × ULN, alkaline phosphatase >2 × ULN, or ALT >3 × baseline [excluding ALT elevation from muscle]) was observed in 31 patients (~37%) treated with delandistrogene moxeparvovec. In 25 of these 31 patients (~81%), the ALI was mild or moderate. The two most severe cases had increased total bilirubin complicated by previously unknown *Helicobacter pylori* and parvovirus infections. Based on the occurrence of ALI in clinical trials of delandistrogene moxeparvovec, this therapy should be postponed in patients with acute liver disease until it is resolved or controlled. Treatment should be carefully considered in patients with preexisting liver impairment or chronic hepatic viral infection, as they may be at a higher risk of serious ALI. Delandistrogene moxeparvovec has not been studied in patients with hepatic impairment, acute liver disease, chronic hepatic condition, or elevated GGT.

Several studies of AAV9-based gene therapies have reported clinical manifestations of complement-mediated thrombotic microangiopathy (TMA), including atypical hemolytic uremic syndrome.[16,42-44] These types of complement-mediated AEs were not observed in delandistrogene moxeparvovec clinical trials. However, patients treated with delandistrogene moxeparvovec demonstrated a predictable, transient, subclinical decrease in complement components C3 and C4 approximately one week postinfusion, which resolved without intervention. Correspondingly, at about one week post-treatment, a similar transient decrease in platelets was observed that improved within two weeks without intervention or clinical manifestations (e.g., TMA or bleeding complications).

Overall, the established safety profile of delandistrogene moxeparvovec within the early-phase clinical trial program was manageable, with no deaths, no AEs that led to study discontinuation, and no AEs known to be associated with complement activation (e.g., TMA).

TABLE 4.
TR-TEAEs Occurring in at Least 15% of All Participants

Most Common TR-TEAEs	1.33×10^{14} vg/kg*,† (n = 73)	All* (N = 85)
Vomiting		
Instances, n	83	98
Patients, n (%)	43 (58.9)	50 (58.8)
Decreased appetite		
Instances, n	40	43
Patients, n (%)	33 (45.2)	36 (42.4)
Nausea		
Instances, n	38	42
Patients, n (%)	29 (39.7)	32 (37.6)
Glutamate dehydrogenase increased		
Instances, n	17	17
Patients, n (%)	16 (21.9)	16 (18.8)
Abdominal pain upper		
Instances, n	15	18
Patients, n (%)	13 (17.8)	15 (17.6)
GGT increased		
Instances, n	14	16
Patients, n (%)	13 (17.8)	15 (17.6)

Abbreviations:
AE = Adverse event
GGT = Gamma-glutamyl transferase
qPCR = Quantitative polymerase chain reaction
TR-TEAE = Treatment-related treatment-emergent AE
vg = Vector genomes
The most frequently reported TR-TEAEs from the delandistrogene moxeparvovec clinical trials Study 101, Study 102, and ENDEAVOR were vomiting, decreased appetite, and nausea.
* For the integrated safety data, the clinical cutoff dates were October 17, 2022, for Study 101; April 1, 2022, for Study 102 (Part 1 only); October 3, 2022, for Study 102 (all available data); and September 19, 2022, for ENDEAVOR. Patients from cohorts 1 to 4 of ENDEAVOR were included.
† In Study 101, all patients received 2.0×10^{14} vg/kg of delandistrogene moxeparvovec, determined by supercoiled standard qPCR (equivalent to 1.33×10^{14} vg/kg using qPCR with linear standard).[39] In Study 102, all patients in Part 1 treated with delandistrogene moxeparvovec received 2.0×10^{14} vg/kg (determined by the supercoiled standard qPCR), which was subsequently found to be equivalent to 1.33×10^{14} vg/kg by linear standard qPCR.[40] Retrospective analysis by linear standard qPCR indicated that 40% of the patients in Part 1 received the 1.33×10^{14} vg/kg dose, 30% received 8.94×10^{13} vg/kg, and 30% received 6.29×10^{13} vg/kg. All patients treated with delandistrogene moxeparvovec in Part 2 received the 1.33×10^{14} vg/kg dose, as determined by linear standard qPCR. In ENDEAVOR, patients received a dose of 1.33×10^{14} vg/kg titrated using linear qPCR.

Conclusions

Delandistrogene moxeparvovec gene therapy is designed to compensate for the absence of dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec microdystrophin, an engineered protein that retains key functional domains of the wild-type protein.

Recommendations for initiating delandistrogene moxeparvovec treatment in patients with DMD (Fig 1) include screening patients for anti-AAVrh74 TAb levels <1:400 with the specific, manufacturer-approved assay to confirm eligibility before infusion with delandistrogene moxeparvovec; ensuring that dosing is sufficiently postponed following cases of viral or bacterial infection and avoiding coadministration with vaccinations; assessing patient baseline liver function (clinical examination, GGT, and total bilirubin), platelet count, and troponin-I levels before administration of delandistrogene moxeparvovec; exercising caution when administering delandistrogene moxeparvovec to patients with elevated liver enzymes at baseline; administering corticosteroids starting one day before infusion (for patients on an existing corticosteroid regimen at baseline) or one week before infusion (for patients not on corticosteroids) and maintaining the corticosteroid regimen for a minimum of 60 days postinfusion, unless earlier tapering is clinically indicated; monitoring liver function weekly for

the first three months following infusion, with continued monitoring until results are unremarkable (normalized or near baseline levels); and monitoring troponin-I levels before infusion and weekly for the first month after infusion, with continued monitoring if clinically indicated.

The safety profile of the delandistrogene moxeparvovec clinical development program has been consistent, monitorable, and manageable. These practical considerations of treatment are based on available clinical trial data and are intended to aid physicians treating patients with DMD.

Declaration of competing interest

Jerry R. Mendell received study funding from Sarepta Therapeutics while at Nationwide Children's Hospital at the time of the study, is currently an employee of Sarepta Therapeutics, and is a co-inventor of AAVrh74.MHCK7.micro-dys technology. Crystal Proud participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock, serves as a speaker for Biogen, and is a principal investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, and Scholar Rock. Craig M. Zaidman receives research support from Biogen and Novartis, served on an advisory board and as a consultant for Sarepta Therapeutics, and received speaker fees from Chugai and Sarepta Therapeutics. Stefanie Mason, Eddie Darton, and Shufang Wang are employees of Sarepta Therapeutics and may have stock options. Christoph Wandel and Alexander P. Murphy are employees of F. Hoffmann-La Roche Ltd and may have stock options. Eugenio Mercuri receives fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd. Francesco Muntoni has received honoraria from Sarepta Therapeutics for participating at symposia and advisory boards and is involved as an investigator in Sarepta Therapeutics' clinical trials. Craig M. McDonald reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, and other consulting fees from Capricor, Catabasis, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, and Sarepta Therapeutics. This study was sponsored by Sarepta Therapeutics, Inc, Cambridge, MA, USA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing and editorial support for the preparation of this manuscript was provided by Jen Ciarochi, PhD, of Nucleus Global and Audrey Vandervelde, PhD, of Sarepta Therapeutics, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp-2022), and was funded by Sarepta Therapeutics, Inc, Cambridge, MA, USA and F. Hoffmann-La Roche Ltd, Basel, Switzerland.

References

1. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9:77–93.
2. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74:637–647.
3. Johnson EK, Zhang L, Adams ME, et al. Proteomic analysis reveals new cardiac-specific dystrophin-associated proteins. PLoS One. 2012;7, e43515.
4. Kole R, Krainer AR, Altman S. RNA therapeutics: beyond RNA interference and antisense oligonucleotides. Nat Rev Drug Discov. 2012;11:125–140.
5. Verhaart IE, Heemskerk H, Karnaoukh TG, et al. Prednisolone treatment does not interfere with 2'-O-methyl phosphorothioate antisense-mediated exon skipping in Duchenne muscular dystrophy. Hum Gene Ther. 2012;23:262–273.
6. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. Muscle Nerve. 2006;34:135–144.
7. Mendell JR, Khan N, Sha N, et al. Comparison of long-term ambulatory function in patients with Duchenne muscular dystrophy treated with eteplirsen and matched natural history controls. J Neuromuscul Dis. 2021;8:469–479.
8. Wahlgren L, Kroksmark AK, Tulinius M, Sofou K. One in five patients with Duchenne muscular dystrophy dies from other causes than cardiac or respiratory failure. Eur J Epidemiol. 2022;37:147–156.
9. Landfeldt E, Thompson R, Sejersen T, McMillan HJ, Kirschner J, Lochmuller H. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. Eur J Epidemiol. 2020;35:643–653.
10. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in duchenne muscular dystrophy: reproduced individual patient data meta-analysis. Neurology. 2021;97:e2304–e2314.
11. Nelson CE, Robinson-Hamm JN, Gersbach CA. Genome engineering: a new approach to gene therapy for neuromuscular disorders. Nat Rev Neurol. 2017;13:647–661.
12. National Library of Medicine. How does gene therapy work?. Available at: https://medlineplus.gov/genetics/understanding/therapy/procedures/; 2022. Accessed December 1, 2023.
13. Viral vectors. Gene therapy Net. Available at: http://www.genetherapynet.com/viral-vectors.html; 2023. Accessed December 1, 2023.
14. Lundstrom K. Viral vectors in gene therapy. Diseases. 2018;6:42.
15. Penaud-Budloo M, Le Guiner C, Nowrouzi A, et al. Adeno-associated virus vector genomes persist as episomal chromatin in primate muscle. J Virol. 2008;82:7875–7885.
16. Muhuri M, Levy DI, Schulz M, McCarty D, Gao G. Durability of transgene expression after rAAV gene therapy. Mol Ther. 2022;30:1364–1380.
17. Asher DR, Thapa K, Dharia SD, et al. Clinical development on the frontier: gene therapy for duchenne muscular dystrophy. Expert Opin Biol Ther. 2020;20:263–274.
18. Lee CS, Bishop ES, Zhang R, et al. Adenovirus-mediated gene delivery: potential applications for gene and cell-based therapies in the new era of personalized medicine. Genes Dis. 2017;4:43–63.
19. Basner-Tschakarjan E, Mingozzi F. Cell-mediated immunity to AAV vectors, evolving concepts and potential solutions. Front Immunol. 2014;5:350.
20. Mingozzi F, High KA. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood. 2013;122:23–36.
21. Goedeker NL, Dharia SD, Griffin DA, et al. Evaluation of rAAVrh74 gene therapy vector seroprevalence by measurement of total binding antibodies in patients with Duchenne muscular dystrophy. Ther Adv Neurol Disord. 2023;16, 17562864221149781.
22. Zygmunt DA, Crowe KE, Flanigan KM, Martin PT. Comparison of serum rAAV serotype-specific antibodies in patients with Duchenne muscular dystrophy, Becker muscular dystrophy, inclusion body myositis, or GNE myopathy. Hum Gene Ther. 2017;28:737–746.
23. Pozsgai ER, Griffin DA, Heller KN, Mendell JR, Rodino-Klapac LR. Systemic AAV-mediated beta-sarcoglycan delivery targeting cardiac and skeletal muscle ameliorates histological and functional deficits in LGMD2E mice. Mol Ther. 2017;25:855–869.
24. Sondergaard PC, Griffin DA, Pozsgai ER, et al. AAV.Dysferlin overlap vectors restore function in dysferlinopathy animal models. Ann Clin Transl Neurol. 2015;2:256–270.
25. Manno CS, Pierce GF, Arruda VR, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med. 2006;12:342–347.
26. Calcedo R, Wilson JM. Humoral immune response to AAV. Front Immunol. 2013;4:341.
27. Hamilton BA, Wright JF. Challenges posed by immune responses to AAV vectors: addressing root causes. Front Immunol. 2021;12, 675897.
28. ELEVIDYS (delandistrogene moxeparvovec) FDA highlights of prescribing information. Available at: https://www.elevidys.com/. Accessed December 1, 2023.
29. UAE Ministry of Health & Prevention. Available at: https://mohap.gov.ae/en/services/registered-medical-product-directory. Accessed December 1, 2023.
30. Potter RA, Griffin DA, Heller KN, et al. Dose-escalation study of systemically delivered rAAVrh74.MHCK7.micro-dystrophin in the mdx mouse model of Duchenne muscular dystrophy. Hum Gene Ther. 2021;32:375–389.
31. Weber T. Anti-AAV antibodies in AAV gene therapy: current challenges and possible solutions. Front Immunol. 2021;12, 658399.
32. Louis Jeune V, Joergensen JA, Hajjar RJ, Weber T. Pre-existing anti-adeno-associated virus antibodies as a challenge in AAV gene therapy. Hum Gene Ther Methods. 2013;24:59–67.
33. Schulz M, Levy DI, Petropoulos CJ, et al. Binding and neutralizing anti-AAV antibodies: detection and implications for rAAV-mediated gene therapy. Mol Ther. 2023;31:616–630.
34. Chicoine LG, Montgomery CL, Bremer WG, et al. Plasmapheresis eliminates the negative impact of AAV antibodies on microdystrophin gene expression following vascular delivery. Mol Ther. 2014;22:338–347.
35. Bönnemann CG, Belluscio B, Braun S, Morris C, Singh T, F M. A collaborative analysis by clinical trial sponsors and academic experts of anti-transgene SAEs in studies of gene therapy for DMD. In: Paper Presented at: Muscular Dystrophy Association (MDA). 2022. Nashville, Tennessee.
36. Bönnemann CG, Belluscio BA, Braun S, Morris C, Singh T, Muntoni F. Dystrophin immunity after gene therapy for Duchenne's muscular dystrophy. N Engl J Med. 2023;388:2294–2296.
37. Khan S, Haegel H, Hollenstein A, et al. T-cell response to micro-dystrophin in a patient treated with delandistrogene moxeparvovec gene therapy: a case of

immune-mediated myositis (P.54). In: Paper Presented at: World Muscle Society (WMS). 2023. Charleston, South Carolina.
38. Potter RA, Cooper-Olson G, Smith ES, et al. Evaluation of safety parameters and dystrophin expression by sequential administration of exon-skipping and gene therapy in a DMD^{mdx} mouse model. In: Paper presented at: World Muscle Society (WMS). 2023. Charleston, South Carolina.
39. Mendell JR, Sahenk Z, Lehman KJ, et al. Long-term safety and functional outcomes of delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy: a phase 1/2a nonrandomized trial. Muscle Nerve. 2024;69:93–98.
40. Zaidman CM, Proud CM, McDonald CM, et al. 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). Ann Neurol. 2023;94:955–968.
41. Mendell JR, Shieh PB, McDonald CM, et al. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. Front Cell Dev Biol. 2023;11, 1167762.
42. Chand DH, Zaidman C, Arya K, et al. Thrombotic microangiopathy following onasemnogene abeparvovec for spinal muscular atrophy: a case series. J Pediatr. 2021;231:265–268.
43. Guillou J, de Pellegars A, Porcheret F, et al. Fatal thrombotic microangiopathy case following adeno-associated viral SMN gene therapy. Blood Adv. 2022;6:4266–4270.
44. Levy D. Complement activation in the setting of gene therapy. Experience with fordadistrogene movaparvovec in Ph1b study of boys with DMD. In: Paper presented at: Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. 2021.