

Drug Use Research & Management Program

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Drug Class Update with New Drug Evaluation: Drugs for Duchenne Muscular Dystrophy

Date of Review: February 2024

Date of Last Review: August 2021

Dates of Literature Search: 01/01/2021 – 11/20/2023

Generic Name: delandistrogene moxeparvovec-rokl
vamorolone

Brand Name (Manufacturer): Elevidys (Sarepta Therapeutics, Inc.)
Agamree (Santhera Pharmaceuticals)

Dossier Received: yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this update is to review place in therapy for 2 agents that were recently approved by the Food and Drug Administration (FDA).

Plain Language Summary:

- People who have Duchenne muscular dystrophy (DMD) slowly lose muscle strength and ability to walk over time.
- Steroids are a type of medicine that can extend the time people are able to walk and delay the need for a wheelchair.
- Prednisone, deflazacort, and vamorolone are 3 steroids that providers can prescribe for people with DMD. Studies do not show that one steroid improves muscle function better than another. All steroids have long-term side effects, and it is difficult to estimate how often these side effects occur. But, some studies show that the amount of people who have a side effect varies based on the medicine.
 - Deflazacort may cause less weight gain than prednisone.
 - Deflazacort may cause more vision problems than prednisone.
 - Vamorolone and prednisone appear to have similar side effects after about 6 months. We need more long-term data to verify if these medicines have different side effects.
- In controlled studies, other medicines have not shown that they improve symptoms or change the course of the disease.
- The Food and Drug Administration (FDA) recently approved a new medicine called a gene therapy for people with DMD. The goal of this medicine is to delay worsening muscle symptoms for people with DMD. However, people who took this medicine had similar muscle function compared to those who did not get the treatment after about 1 year.
- The FFS Oregon Health Plan will currently pay for prednisone. Before Oregon FFS Medicaid will pay for other medicines in people with DMD, the provider must send in additional information to the Oregon Health Authority. This process is called prior authorization (PA).
- We recommend adding new medicines for DMD to this policy.

Research Questions:

1. What is the comparative efficacy or effectiveness of therapies for Duchenne muscular dystrophy (DMD) based on symptom improvement, muscle or pulmonary function, quality of life, or disease progression?
2. What is the comparative safety of therapies for people with DMD?
3. What is the efficacy and safety of vamorolone compared to other corticosteroids for the treatment of people with DMD?
4. What is the evidence evaluating efficacy and safety of delandistrogene moxeparvovec for people with DMD?
5. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for DMD?

Conclusions:

- This class update includes one systematic review, evaluations of 2 new drugs, and one comparative randomized controlled trial (RCT).
- The systematic review identified insufficient evidence that exon skipping therapies improve muscle or pulmonary function compared to standard of care.¹ Evidence was limited by lack of controlled trials. Confirmatory, randomized placebo-controlled trials for exon skipping therapies have not been completed.
- A new corticosteroid, vamorolone, was approved by the Food and Drug Administration (FDA) for DMD based on a single, placebo-controlled, active-comparator RCT.
 - Compared to placebo at 24 weeks, vamorolone 6 mg/kg/day improved multiple motor function tests including the time to stand from a supine position (difference in velocity of 0.06 rises/second; 95% CI 0.02 to 0.10; p=0.002) and the distance walked in 6 minutes (mean difference 41.6 meters; 95% CI 14.2 to 68.9) and mean time to run or walk 10 meters (mean difference of 0.4 miles/hour or 0.24 meters/second; 95% CI 0.09 to 0.39; p=0.002) based on low quality evidence.² These differences achieved values thought to be related to minimum clinically important changes referenced in the literature.
 - Compared to prednisone, vamorolone had similar motor function changes in people with DMD over 24 weeks based on low quality evidence.² Vamorolone has similar safety concerns as other corticosteroids.^{2,3} Safety concerns include immunosuppression, alterations in endocrine, cardiac and renal function, behavior and mood disturbances, effects on bone, delays in growth, and ophthalmic effects.⁴ There is insufficient information to evaluate whether vamorolone and prednisone have different effects on risk of fracture, growth, or development in people with DMD.³
- A trial evaluating use of corticosteroids in people with DMD given daily deflazacort and prednisone given daily have comparable muscle and pulmonary function after 3 years.⁵ Daily corticosteroid regimens were better at preserving muscle function than intermittent prednisone use.⁵
- There is insufficient evidence that the gene therapy, delandistrogene moxeparvovec, improves muscle function in ambulatory patients 4 to 7 years of age with DMD over 48 weeks compared to placebo.⁶ There was no statistical difference in the North Star Ambulatory Assessment (NSAA) score at 48 weeks with delandistrogene moxeparvovec compared to placebo (change from baseline of 1.7 vs. 0.9 points; least square mean difference [LSMD] 0.8; 95% confidence interval [CI] -1.03 to 2.67; p=0.37).⁶ Secondary timed motor function tests were also no different between groups.⁶ FDA approval was based on a post-hoc, subgroup analysis in people 4-5 years of age.
- Safety concerns identified with this gene therapy include acute liver injury, thrombocytopenia, immune-mediated myositis, and myocarditis.⁷ Prednisone 1 to 1.5 mg/kg/day is administered one day prior to treatment and for 60 days post-treatment to decrease the risk of an immune response.⁷ Therapy is contraindicated in patients with deletions involving exon 8 or 9, and patients with deletions in exons 1 to 17 or exons 59 to 71 of the DMD gene may be at increased risk for myositis.⁷ Patients administered delandistrogene moxeparvovec also demonstrated a persistent immune response to the viral capsid which is expected to cross-react with other vectors of different serotypes and could preclude use of any future gene therapy.⁸

Recommendations:

- Implement prior authorization criteria for delandistrogene moxeparvovec to limit use to the FDA approved indication.
- Update prior authorization criteria to include all non-preferred corticosteroids for DMD.
- No changes to the preferred drug list (PDL) are recommended for corticosteroids based on clinical evidence.
- After evaluation of costs in executive session, deflazacort, vamorolone, and all targeted therapies were made non-preferred.

Summary of Prior Reviews and Current Policy

Therapies approved by the United States (US) Food and Drug Administration (FDA) for treatment of DMD were last reviewed by the Pharmacy and Therapeutics (P&T) Committee in February and August 2021.

- Corticosteroids are recommended as a first-line treatment for patients with DMD. Prior reviews have identified insufficient evidence to determine differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions.^{9,10} Evidence was limited by small sample sizes, high or unclear risk of bias, incomplete outcome reporting, and inadequate data in a population of US patients.^{9,10}
- Exon-skipping treatments were approved by the FDA based on changes in dystrophin protein from baseline, and confirmatory studies have not been completed. Current evidence demonstrates no difference in motor function outcomes for exon-skipping therapies (e.g., casimersen, eteplirsen, golodirsen, viltolarsen) compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes.
- Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 2**). Prednisone is available without PA.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.¹¹ In the US, it is estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,^{11,12} and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.¹³ Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Disease progression varies considerably based on individual factors, and patients with Becker muscular dystrophy generally have less severe symptoms than people with DMD. Long-term complications for people with DMD include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.¹¹ In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which was attributed to improvements in supportive care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.¹⁴ Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.¹⁴ The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.¹⁴

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Non-pharmacological therapies are often essential in disease management, and include physical therapy and use of support devices such as braces and wheelchairs.¹¹ As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.¹¹ Available drug treatments include corticosteroids and exon-skipping therapies. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.^{11,15} Corticosteroids are often continued if patients become non-ambulatory,

though the continued benefits are less clear with progressive disease.¹¹ Some of the most common steroid regimens include prednisone 0.75 mg/kg/day, deflazacort 0.9 mg/kg/day, or intermittent prednisone 0.75 mg/kg for 10 day on and 10 days off for people unable to tolerate daily dosing.⁵

Exon-skipping therapies have been approved based on changes in dystrophin protein. The theoretical goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.¹⁶ Each therapy is intended to target a specific mutation. Eteplirsen was approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.¹⁷ In 2019 and 2020, golodirsen and viltolarsen were approved for patients with mutations amenable to exon 53 skipping (thought to represent about 8% of the DMD population or approximately 1200 patients in the US).¹⁸ Most recently, casimersen was approved for patients with mutations amenable to exon 45 skipping. All therapies have the same mechanism of action and are administered as weekly intravenous infusions.

While eteplirsen and golodirsen have shown a slight increase in dystrophin (with increased dystrophin levels remaining at less than 1% of normal), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.^{19,20} In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test (6MWT) at 24 or 48 weeks compared to placebo. Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen or casimersen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.¹⁸ While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.²¹⁻²⁴ Because natural history studies have shown that disease progression with DMD varies significantly based on a variety of individual patient factors, these uncontrolled or historical-controlled studies have limited utility in evaluating drug efficacy.⁸ Without adequate randomization, studies cannot control for unknown confounding factors which may impact disease progression. Similarly, risk of performance and detection bias is increased for unblinded and uncontrolled studies that evaluate motor function tests since results are highly dependent on procedure (method of administration) and motivation of the patient. Data from open-label studies generally show greater improvement than data from blinded studies because open-label studies are unable to control for differences in test administration and patient effort.⁸ Confirmatory post-marketing, randomized trials have not been completed for any exon skipping therapies.

There is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement, and available thresholds cited in the literature are currently based on expert opinion. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.²⁵ Experts suggest that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.²⁵ Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.^{25,26} In patients with Becker muscular dystrophy, a less severe form of muscular dystrophy, dystrophin protein levels are on average 80% of normal.²⁵ An FDA analysis evaluating the change in 6MWT per year and dystrophin level changes associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that small increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.¹⁸

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used to assess motor function and strength in patients with DMD including timed functional tests and scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34).^{27,28} It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2

scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. In people with DMD, natural history studies have shown that, with standard of care alone, muscle function usually continues to improve in patients who are 4 to 6 years of age.⁸ In 395 patients identified from the North Star Clinical Network database, NSAA scores increased by about 3 points per year until an average of 6.3 years (peaking at an NSAA score of 26) and declined by about 3 points per year for subsequent years.⁸ However, there was significant heterogeneity among patients. In people with DMD, NSAA scores had decreased to less than or equal to 5 points in about 25% of people by age 10, in 35% of people by age 12, in 21% of people by age 14, and scores remained greater than 5 points in 19% of people beyond 15 years of age.⁸

Other standard timed functional tests include time to climb 4 stairs, time to walk 10 meters, time required to stand from a supine position, and the 6MWT which evaluates distance traveled in 6 minutes.²⁹ One publication, with notable potential conflicts of interest with a drug manufacturer, correlated clinician-rated scores of disease severity to changes in timed functional tests to define minimum clinically important differences (MCID) for ambulatory patients with DMD.³⁰ Authors use data from natural history studies to compare times on these functional tests to differences of at least one point on the Vignos lower extremity scale.³⁰ The Vignos scale is a validated 8 item clinician-rated score which evaluates a patient's ability to walk, rise from a chair, and climb stairs with or without assistance. Scores range from one (walks and climbs stairs without assistance) to 4 (walks unassisted and rises from chair but cannot climb stairs) to 8 (participant is in bed at all times).³⁰ They concluded that in the 10 meter walk test, a decline of 0.21 meters/second corresponded to a one point change in the Vignos scale over 12 months.³⁰ Similarly minimum differences of 0.023 rises/second in the time to stand from supine and 0.035 tasks/second in the time required to climb 4 stairs corresponded to one point change on the Vignos scale over 12 months for patients with DMD who are ambulatory.³⁰ However, these MCID values may vary depending on the baseline ambulatory function of a population. In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.^{24,31,32} The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.²⁹ NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.²⁸ The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes. Like all motor function assessments, NSAA score is often very dependent on motivation.²⁵

Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).^{33,34} However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to clinical outcomes such as need for mechanical ventilation or airway clearance.³³

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A 2022 DERP systematic review evaluated exon-skipping therapies for DMD.¹ The review evaluated evidence from RCTs, uncontrolled interventional studies and cohort studies with at least 20 participants published through February 2022. Clinical outcomes in interest included adverse events, mortality, and tests for cardiac, pulmonary and motor function. The review identified 11 studies evaluating eteplirsen (n=6), golodirsen (N=1), viltolarsen (N=3), and casimersen (n=1).¹ Most of the data was from non-randomized and uncontrolled studies or studies with only a historical control. Only one placebo-controlled RCT was identified for each drug, and only one RCT (for eteplirsen) evaluated clinical outcomes of interest compared to placebo. Evidence was graded as insufficient for all safety and efficacy outcomes reflecting substantial uncertainty in the treatment effects.¹

- Motor function:
 - In the single RCT evaluating effectiveness of eteplirsen compared to placebo, motor function (assessed with the 6MWT) declined from baseline with no difference compared to placebo.¹
 - In uncontrolled studies for eteplirsen and golodirsen, motor function declined from baseline with no comparable control group to determine if decline was slower with treatment.¹
 - In uncontrolled studies of viltolarsen, there were mixed results for motor function. In one study, motor function improved or remained stable at 25 weeks, and motor function declined over 24 weeks in another study.¹ There were differences in age between participants enrolled in these trials, which may explain some of the observed variability in motor function.
 - No identified studies evaluated motor function for casimersen.¹
- Pulmonary function:
 - In 5 uncontrolled studies of eteplirsen, pulmonary function declined from baseline with no comparable control group to determine if decline was slower with eteplirsen.¹ Similar decline was observed in one uncontrolled study of golodirsen.¹
 - No identified studies evaluated pulmonary function for viltolarsen or casimersen.
- Adverse events:
 - In the single RCT evaluating eteplirsen compared to placebo, there was no difference in adverse events between groups.¹
 - In uncontrolled studies, most participants experienced at least one adverse event, but few serious adverse events were reported.¹
 - There were no deaths reported during these studies.¹

New Guidelines:

No new high-quality guidelines were identified since the last review.

New Formulations or Indications:

No new formulations or expanded indications were identified since the last review.

New FDA Safety Alerts:

FDA labeling for casimersen (Amondys 45®) was updated in March 2023 to include risk of hypersensitivity reactions including angioedema and anaphylaxis based on post-marketing reports.³⁵ Similar language is also included in FDA labeling for eteplirsen (Exondys 51®).¹⁹

Randomized Controlled Trials:

A total of 40 citations were manually reviewed from the initial literature search. After further review, all except one RCT was excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). This trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Guglieri, et al. 2022. ⁵ NCT01603407 DB, PG, RCT N=196 Duration: 3 years	1. Prednisone 0.75 mg/kg daily 2. Deflazacort 0.9 mg/kg daily 3. Prednisone 0.75 mg/kg intermittent (10 days on/10 days off)	Genetically confirmed DMD, age 4 to 7 years, who were treatment-naïve to corticosteroids Jan 2013 to Oct 2019 32 clinics in 5 countries (Canada, Germany, Italy, the UK, and the US). 42% were from the US.	Composite of: • Rise from floor velocity • FVC • Participant/parent TSQM global satisfaction score Values were averaged for all follow-up visits through 36 months. Follow-up visits occurred at 3 months, 6 months, then every 6 months until 3 years.	Rise from floor (rises/s) 1. 0.236 (95% CI 0.219 to 0.253) 2. 0.240 (95% CI 0.223 to 0.258) 3. 0.180 (95% CI 0.163 to 0.197) 1 vs. 2: MD -0.004 (95% CI -0.03 to 0.02); NS 1 vs. 3: MD 0.06 (95% CI 0.03 to 0.08); p=0.003 2 vs. 3: MD 0.06 (95% CI 0.03 to 0.09); p=0.017 FVC (liters) 1. 1.44 (95% CI 1.38 to 1.50) 2. 1.40 (95% CI 1.34 to 1.46) 3. 1.46 (95% CI 1.40 to 1.52) 1 vs. 2: MD 0.04 (95% CI -0.06 to 0.14); NS 1 vs. 3: MD -0.02 (95% CI -0.12 to 0.08); NS 2 vs. 3: MD -0.06 (95% CI -0.16 to 0.04); NS TSQM global satisfaction score (range 0-100) 1. 71.2 (95% CI 66.8 to 75.7) 2. 67.8 (95% CI 63.2 to 72.4) 3. 65.1 (95% CI 60.6 to 69.5) 1 vs. 2: MD 3.5 (95% CI -3.7 to 10.6); NS 1 vs. 3: MD 6.2 (95% CI -0.9 to 13.2); NS 2 vs. 3: MD 2.7 (95% CI -4.4 to 9.8); NS Secondary motor function outcomes (6MWT, 10m run/walk time, NSAA score) were not different for daily regimens, but were improved with daily regimens compared to intermittent dosing.	<i>There was no difference in primary or secondary motor outcomes for daily deflazacort or prednisone. Participants on daily regimens had improved motor outcomes compared to intermittent prednisone dosing.</i> Attrition was similar between groups (14%). Medication supply issues necessitated a temporary switch to prednisone for 74 people in 2017 and unblinding of 4 participants in the intermittent prednisone group. Of 229 people screened, 196 were randomized. Most common reason for ineligibility was inability to maintain reproducible FVC (10%). Most participants (74-90%) in each group identified as White. 14-21% identified as Hispanic; other races were underrepresented. AEs that were ≥5% more frequent with daily prednisone vs. deflazacort: URI, abdominal pain, weight gain, influenza, skin papilloma. AEs that were ≥5% more frequent with daily deflazacort vs. daily prednisone: musculoskeletal pain,

					sleep disturbance, limb injury, joint pain, and cataracts.
Abbreviations: 6MWT = 6-minute walk test; AE = adverse events; CI = confidence interval; DB = double blind; DMD = Duchenne muscular dystrophy; FVC = forced vital capacity; m = meter; MD = mean difference; NSAA = North Star Ambulatory Assessment; PG = parallel group; RCT = randomized controlled trial; s = second; TSQM = treatment satisfaction questionnaire for medication; UK = United Kingdom; URI = upper respiratory infection; US = United States					

NEW DRUG EVALUATION: Vamorolone

See **Appendix 4 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Vamorolone is a corticosteroid which was FDA approved for the treatment Duchenne muscular dystrophy in people at least 2 years of age.⁴ The recommended maintenance dose is 6 mg/kg/day which can be titrated down based on tolerability. The primary trial used for FDA approval was a multicenter phase 2b trial evaluating vamorolone 6 or 2 mg/kg/day compared to prednisone 0.75 mg/kg/day or placebo over 24 weeks (**Table 4**).² Enrolled patients (n=121) were 4 to 7 years of age and identified primarily as White and non-Hispanic.² Pharmacology data from an open-label study was used to support FDA-approval down to 2 years of age.³ Enrolled patients had to be able to walk unassisted and stand from a supine position in less than 10 seconds. People were excluded if they had a variety of comorbid conditions including symptomatic cardiomyopathy, immunosuppression, diabetes, or history of systemic fungal/viral infections.²

The trial used adequate methods for randomization and allocation concealment, but groups were small and had imbalances in baseline characteristics which could impact results. In particular, patients randomized to prednisone had better motor function tests than those randomized to vamorolone.² There were also clinically important differences in the 6MWT for patients randomized to placebo compared to vamorolone groups (placebo 355 m vs. vamorolone 313 m), and mean values for other motor function tests were slightly better than vamorolone 6 mg/kg group, though the exact impact of these differences is unknown.² The trial used a double dummy design, but the specific methods used to blind treatments was not reported making risk for performance and detection bias unclear. Accommodations were also made during the COVID pandemic in order to collect some tests remotely. About 10% of 24-week assessments for time to stand from a supine position were conducted remotely by family and video recorded for assessment by providers.² Secondary outcomes were not collected during the pandemic for 15% (n=17) of 6MWT and 12% (n=14) of assessments for time to run/walk 10 meters.² Imputation methods for missing data were not reported leading to unclear risk for attrition bias for secondary outcome measures. However, attrition rates were similar between groups and multiple sensitivity analyses to assess the impact of missing data confirmed the results from the primary analyses.³

The primary outcome was the time to stand from supine with vamorolone 6 mg/kg/day compared to placebo (measured in velocity [rises per second]). A variety of other motor function tests were evaluated in the study including the 6MWT, time to run or walk 10 meters, NSAA, and time to climb 3 stairs. Strength assessments and parent-reported outcomes were also evaluated. Secondary outcomes were analyzed in a hierarchical testing method. At 24 weeks, the time to stand from a supine position was improved with vamorolone 6 mg/kg/day (mean change of 0.05 rises/s) compared to placebo (mean change of -0.01 rises/s; difference 0.06 rises/s; 95% CI 0.02 to 0.10; p=0.002).² Similar improvement was observed for 2 mg/kg/day compared to placebo. The 6MWT was improved with both vamorolone doses compared to placebo with mean differences of 41.6 m (95% CI 14.2 to 68.9) and 37.1 (95% CI 9.6 to 64.7) for 6 and 2 mg/kg/day, respectively.² These results meet thresholds for clinically important differences that are referenced for the 6MWT (MCID of 30 m) and time to stand from supine

(MCID 0.02 rises/s), but differences in baseline motor function assessments decrease certainty that these differences are due to treatment alone. Vamorolone 6 mg/kg/day also had improved time to run/walk 10 meters compared to placebo (mean difference of 0.4 miles/hr or 0.24 m/s; 95% CI 0.09 to 0.39; $p=0.002$), but results for the 2 mg/kg/day group were not statistically significant compared to placebo.² Other motor function outcomes were considered exploratory based on the hierarchical testing pattern. Changes in motor function tests were apparent after 6 weeks of treatment and continued to improve over 24 weeks.² Subgroup analyses based on age, race, country, and baseline time to stand from supine were generally consistent with the overall treatment effects for motor outcomes.³

Specific results for motor function tests were not reported for prednisone, but were described as no different than vamorolone 6 mg/kg/day.² Vamorolone 2 mg/kg/day was less effective than prednisone 0.75 mg/kg/day for time to run/walk 10 meters and time to climb 3 steps, but had similar outcomes for time to stand from supine, 6MWT, and NSAA scores.²

Limitations in the evidence include lack of long-term efficacy data and lack of data for patients with lower functional scores. Corticosteroids are generally recommended as a first-line treatment option for patients with DMD to prevent disease progression and preserve motor function. This study only included participants who were 4 to 7 years of age, and the efficacy of vamorolone in people with more progressive disease is unknown. Prednisone and deflazacort are the most common corticosteroids used in people with DMD and there are no direct comparisons to deflazacort. Specific results for prednisone were not analyzed in this study and comparisons were described only generally. People who identified with a non-White racial group were underrepresented in this study.

Clinical Safety:

Vamorolone has many of same adverse events and safety concerns as other corticosteroids. Warnings and precautions for all corticosteroids include alterations in endocrine function (e.g., Cushing's syndrome, hyperglycemia and adrenal insufficiency with withdrawal), immunosuppression and effects on vaccine efficacy and safety, behavior and mood disturbances, effects on bones, ophthalmic effects, delayed growth and development, changes in cardiovascular and renal function, gastrointestinal perforations, Kaposi's sarcoma, myopathy, and thromboembolic events.⁴ *In vitro* studies have suggested that vamorolone has some activity as a mineralocorticoid antagonist. However, there is insufficient data from clinical studies to demonstrate that risk for cardiovascular or renal adverse effects differ with vamorolone compared to other corticosteroids.³

The phase 2b trial also evaluated laboratory markers of bone turnover. These markers indicate that, like other corticosteroids, vamorolone is associated with increased risk of bone turnover and fracture risk in a dose dependent manner.³ This is supported by data from open-label extension studies in which bone fractures occurred in 2% ($n=2$) of patients receiving vamorolone 2 mg/kg/day and 7% ($n=7$) of patients receiving 6 mg/kg/day.³ Two patients (2%) treated with vamorolone 6 mg/kg/day had spinal compression fractures in the study extension period.³ Compared to prednisone, patients treated with vamorolone had a lower rate of bone turnover markers and improved height percentile for their age.³ However, imbalances in baseline height percentile increase risk of selection bias.² Height percentile for age was 23% for vamorolone 6 mg/kg/day, 30% for vamorolone 2 mg/kg/day, 37% for prednisone, and 33% for placebo.² Studies were also conducted only over a short period, were not powered to detect differences between groups, and were not designed to control for multiplicity for these outcomes. Furthermore, the association of these bone turnover markers on fracture risk is unknown, and additional data are needed to quantify comparative fracture risk with different corticosteroids.

In clinical trials, the most common adverse events occurring in more than 10% of patients and more common than placebo included Cushingoid features, psychiatric disorders, vomiting, weight increases, vitamin D deficiency (**Table 2**).⁴ Compared to prednisone, vamorolone has similar adverse effects.

Table 2. Adverse events occurring in more than 5% of patients and more common than placebo⁴

	Vamorolone 2 mg/kg/day (%)	Vamorolone 6 mg/kg/day (%)	Prednisone 0.75 mg/kg/day (%) ³	Placebo (%)
Cushingoid features	7	29	23	0
Psychiatric disorders	7	21	32	14
Irritability ³	0	11	3	0
Vomiting	17	14	3	7
Fall ³	7	11	13	3
Weight increased	0	11	13	3
Vitamin D deficiency	7	11	3	0
Cough	10	7	10	3
Headache	7	7	3	3
Diarrhea	3	7	7	3
Increased appetite	3	7	3	3
Rhinitis	3	7	0	3

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
- 2) Disease progression
- 3) Quality of life
- 4) Mortality
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Time to stand from a supine position (motor function)

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Corticosteroid which binds to the glucocorticoid receptor to cause anti-inflammatory and immunosuppressive effects.
Oral Bioavailability	After administration with food, the median Tmax is ~2 hours. A high fat or high calorie meal reduces Cmax by 18% and AUC by 13%, and delays Tmax by about 1 hour.
Distribution and Protein Binding	Vd = 162 L for a patient with DMD weighing 20 kg Protein binding 81% <i>in vitro</i> with a blood to plasma ratio of 0.87.
Elimination	Clearance of 58L/hr in a person with DMD who is 20 kg. Excreted 30% in feces (15% as metabolites), 48% in urine (>99% as metabolites).
Half-Life	2 hours
Metabolism	Metabolized via CYP3A4/5, CYP2C8, UGT1A3, UGT2B7, UGT2B17.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; DMD = Duchenne muscular dystrophy; hr = hour; kg = kilogram; L = liter; T_{max} = time to maximum concentration; V_d = volume of distribution

Table 4. Comparative Evidence Table for Vamorolone.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Guglieri, et al. 2022. ² Phase IIb, AC, DB, double-dummy, PC, cross-over, RCT NCT0343 9670	1. Vamorolone 6 mg/kg/day suspension 2. Vamorolone 2 mg/kg/day suspension 3. Prednisone tablets 0.75 mg/kg/day 4. Placebo tablets Period 1: 24 wks Period 2: 24 wks In period 2, people receiving prednisone or placebo switched to vamorolone	<u>Demographics:</u> - Mean age: 5 yrs - BMI: 16.2-16.8 mg/kg - TTSTAND velocity: 0.18-0.22 rises/s - 6MWT: 313-355 m - TTRW 10 m velocity: 1.6-1.9 m/s - NSAA: 17-21 - Mean height percentile: 23% (vamorolone 6 mg/kg) to 37% (prednisone) <u>Key Inclusion Criteria:</u> - DMD gene loss-of-function variation or lack of muscle dystrophin - Age: 4-6 years (inclusive) - Time to stand from supine < 10 s without assistance - Ability to walk independently - Weight 13-39.9kg - Chicken pox immunity - Normal clinical laboratory testing <u>Key Exclusion Criteria:</u> - Renal, hepatic disease, immunosuppression, diabetes, current or h/o chronic systemic fungal or viral infections, primary aldosteronism, symptomatic cardiomyopathy, cognitive or behavioral problems	<u>ITT:</u> 1. 30 2. 30 3. 31 4. 30 <u>PP:</u> 1. 27 2. 28 3. 30 4. 28 <u>Attrition:</u> 1. 2 (7%) 2. 2 (7%) 3. 1 (3%) 4. 2 (7%)	<u>Primary Endpoint:</u> Change from baseline to 24 weeks Mean TTSTAND velocity 1. 0.05 (SE 0.07) rises/s 2. 0.04 (SE 0.09) rises/s 3. NR 4. -0.01 (SE 0.06) rises/s 1 vs. 4: 0.06 rises/s (95% CI 0.02 to 0.10); p=0.002 2 vs. 4: 0.05 rises/s (95% CI 0.01 to 0.08); p=0.02 <u>Secondary Endpoints:</u> Mean 6MWT 1. 28.8 (SE 49.7) m 2. 31.0 (SE 51.1) m 3. NR 4. -23.9 (SE 59.6) m 1 vs. 4: 41.6 m (95% CI 14.2 to 68.9); p=0.003 2 vs. 4: 37.1 m (95% CI 9.6 to 64.7); p=0.009 Mean TTRW 10 m (velocity) 1. 0.28 (SE 0.28) m/s 2. 0.16 (SE 0.23) m/s 3. NR 4. 0.02 (SE 0.33) m/s 1 vs. 4: 0.24 m/s (95% CI 0.09 to 0.39); p=0.002 2 vs. 4: 0.13 m/s (95% CI -0.03 to 0.28); p>0.05 Results for prednisone were described only generally.	NA NA NA NA NA NS	<u>Treatment-emergent AE</u> 1. 89.3% 2. 83.3% 3. 83.9% 4. 79.3% <u>Discontinuations due to AE</u> 1. 0 (0%) 2. 0 (0%) 3. 1 (3%) 4. 0 (0%) <u>Serious AE</u> 1. 0 (0%) 2. 1 (3%) 3. 1 (3%) 4. 0 (0%) <u>Change from baseline in height percentile</u> 1. 3.86% (SE 6.16) 2. 0.26% (SE 9.22) 3. -1.88% (SE 8.81) 4. NR 1 vs. 3: 4.98% (95% CI 0.75 to 9.21); p=0.02 2 vs. 3: 1.86% (95% CI -2.27 to 6.00); p>0.05 <u>BMI z score</u> 1. 0.52 (SE 0.62) 2. 0.40 (SE 0.45) 3. 0.41 (SE 0.51) 4. NR p>0.05	NA NS NS NA NS NS	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> High. Adequate randomization and allocation concealment methods used via IWRS. Baseline motor function differed between groups (most tests were better with prednisone and some were better with placebo than vamorolone). <u>Performance Bias:</u> Unclear. Blinded with double dummy design. Method of blinding NR. <u>Detection Bias:</u> Unclear. Method of blinding was NR. <u>Attrition Bias:</u> Low. The number of people who withdrew from the study was small. Primary outcome data was conducted remotely for 10% of assessments, but the COVID pandemic resulted in missing data for other secondary endpoints. Multiple sensitivity analyses evaluating the impact of missing data demonstrated similar results. <u>Reporting Bias:</u> Low. Outcomes reported as pre-specified in the statistical analysis plan. Efficacy outcomes for prednisone were NR in detail. <u>Other Bias:</u> Low. Study was grant funded through partnerships with NIH and multiple patient organizations. Funders had no role in the study design or data analysis. Authors report grant support, honoraria, personal fees and consulting fees from various pharmaceutical companies outside the submitted work. Two authors reported personal fees from the manufacturer of vamorolone. Applicability: <u>Patient:</u> 83% of participants were White and 96% were not Hispanic or Latino. Other racial groups were under-represented. Most applicable for young people (4-7 years old) who retain motor function. The mean 6MWT was over 300m (normal range 400-700m) and members were required to be able to stand from a supine position in <10s. Efficacy in people with more severe disease is unknown. <u>Intervention:</u> Dose response observed for motor function outcomes. Recommended FDA-dose of vamorolone is 6 mg/kg/day. Lower doses may be less effective than prednisone for some motor outcomes. <u>Comparator:</u> Placebo appropriate to evaluate efficacy. Efficacy outcomes compared to prednisone, the current standard of care, were only briefly described.

		<ul style="list-style-type: none"> - Prior oral steroid or immunosuppressant use for > 1 month - Other therapy for DMD within 3 months 		<p>Vamorolone 6 mg/kg/day and prednisone were similar for all motor outcomes.</p> <p>Vamorolone 2 mg/kg/day was similar for TTSTAND, 6MWT, & NSAA but less effective than prednisone for TTRW and TTCLIMB.</p>			<p>Outcomes: Relatively short-term study. Outcomes for second period of the study (switching to vamorolone) are not yet reported.</p> <p>Setting: 33 centers in 11 countries in Europe and the US from June 29, 2018, to February 24, 2021. About 44% of enrolled patients were from the US.³</p>
<p>Abbreviations: 6MWT = 6 minute walking test; AC = active control; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DB = double blind; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; h/o = history of; ITT = intention to treat; IVWRS = interactive voice/web response system; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; NSAA = North Star Ambulatory Assessment; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; s=seconds; SE = standard error; TTCLIMB = time to climb 3 steps; TTSTAND = time to stand from supine; TTRW = time to run/walk 10 meters</p>							

NEW DRUG EVALUATION: Delandistrogene moxeparvovec

See **Appendix 4 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Delandistrogene moxeparvovec is an adeno-associated viral vector-based gene therapy that was approved by the FDA in 2023 under the accelerated approval pathway. It is a one-time treatment indicated for patients with Duchenne muscular dystrophy who are ambulatory, 4 to 5 years of age, and have a confirmed mutation in the DMD gene.⁷ The viral capsid contains a gene for an engineered, shortened micro-dystrophin protein.⁸ Because the gene encoding wild-type dystrophin is the largest known human gene, it cannot be delivered in a viral capsid. Instead, the viral capsid contains a micro-dystrophin protein containing select domains of normal dystrophin. This micro-dystrophin was based on protein identified in a patient with a milder form of the disease called Becker muscular dystrophy.⁸ Micro-dystrophin proteins are not normally expressed in any patients, and it is not known if expression correlates with improved symptoms or a reduction in disease progression.⁸ There is increasing literature which shows that dystrophin may play an important scaffolding role to recruit additional proteins necessary for normal muscle function such as ion channels, kinases, and neuronal nitric oxide synthase.⁸ However, due to size constraints of the viral vector, the dystrophin protein regions responsible to these functions were not included in the micro-dystrophin formed by delandistrogene moxeparvovec.⁸ Because the form of micro-dystrophin gene included in delandistrogene moxeparvovec is based on a form of dystrophin present in people with milder symptoms, this gene therapy is not designed to prevent or cure the disease. The goal of this gene therapy is to reduce symptom severity.

Several trials were reviewed by the FDA for approval. Because of the heterogeneous nature of DMD and significant risk of bias with the use of external controls, the FDA primarily focused on information from a phase 2, placebo-controlled, crossover RCT to evaluate efficacy of delandistrogene moxeparvovec.⁸ The phase 2 RCT included 41 patients randomized to one-time treatment or placebo.⁶ After 48 weeks, patients were crossed over to the alternate treatment group which allowed participants initially randomized to placebo to receive therapy. Even though trial remained blinded, after the crossover at 48 weeks, all patients had received treatment, making the study essentially non-controlled. Data from this RCT was supplemented by information from uncontrolled, single-arm studies. The co-primary endpoints for this trial were change in micro-dystrophin protein expression at 12 weeks and change in NSAA score at 48 weeks.⁶ Secondary clinical endpoints included other timed motor function tests such as time to run/walk 10 meters, 100 meter run/walk time, time to climb 4 stairs, and time to

stand from a supine position. Patients included in the trial were 4 to 8 years of age (inclusive) and had a confirmed mutation in the DMD gene resulting in a frameshift between exons 18 and 58.⁶ Patients were ambulatory and on a stable dose of corticosteroids for at least 12 weeks. Patients were excluded if they had cardiomyopathy, elevated gamma-glutamyl transferase, or elevated creatinine which may limit applicability to patients with more severe disease.⁶

At 12 weeks, patients administered delandistrogene moxeparvovec had an increase in micro-dystrophin expression compared to placebo (change from baseline of 23.8% vs. 0.14%; $p=0.0001$).⁶ Micro-dystrophin was measured with Western blot and reported as a percentage of normal levels. For patients treated in the first cohort, micro-dystrophin expression was maintained at 60 weeks (19% of normal levels).⁶ However, this difference did not correlate with clinical endpoints. There was no statistical difference in NSAA score at 48 weeks with delandistrogene moxeparvovec compared to placebo (change from baseline of 1.7 vs. 0.9 points; LSMD 0.8; 95% CI -1.03 to 2.67; $p=0.37$).^{6,8} Secondary timed motor function tests were also no different between groups.⁶

Data from the first 48 weeks of the phase 2 trial was limited by risk for selection bias due to imbalances in motor function tests at baseline. Patients randomized to treatment with delandistrogene moxeparvovec in the first 48 weeks had lower NSAA scores than patients randomized to placebo (mean score of 19.8 vs. 22.6).⁶ The time required to perform other motor function tests was also slightly longer for patients randomized to delandistrogene moxeparvovec. A post-hoc analysis identified that baseline disparities between groups were more apparent for patients 6-7 years of age.⁶ Subgroup analyses for patients 4-5 years of age ($n=8$) identified more balanced motor function at baseline and provided support for FDA approval. In patients 4-5 years of age ($n=16$), NSAA score improved by 4.3 points (SD 0.7) at 48 weeks with delandistrogene moxeparvovec compared to a 1.9 (SE 0.7) point improvement with placebo.⁶ In patients 6-7 year of age ($n=25$), NSAA score declined with delandistrogene moxeparvovec compared to an improvement for patients receiving placebo (LSMD -0.2 [SE 0.7] vs. 0.5 [SE 0.7]).⁸ However, these post-hoc subgroup analyses were conducted without a pre-specified testing plan to control for multiplicity and type 1 error.⁸ This increases risk for reporting bias and decreases confidence that the results observed in these subgroup are representative of the true treatment effect.

Current studies show no correlation between change in micro-dystrophin at 12 weeks and functional improvement for patients treated with delandistrogene moxeparvovec. After a change in the analytic process during the clinical trial program, it was retrospectively identified that only 8 patients received the intended study dose in the first 48 weeks of the phase 2 trial.⁸ Six patients received about two-thirds of the intended dose and 6 patients received about half the intended dose.⁸ At 12 weeks, a dose response was observed for micro-dystrophin expression for members who received low dose, middle dose, and intended dose respectively (mean levels of 3.6% [SD 5.7%], 28.2% [SD 52.2%], and 43.4% [SD 48.6%], respectively).⁸ However, there was no commensurate change in functional improvement based on dose received.

Available studies show that there is a persistent immune response to viral capsids after administration of delandistrogene moxeparvovec.⁸ This immune response is expected to cross-react with other adeno-associated viral vectors of different serotypes and could result in immunity to any future gene therapies.⁸ Because of this immune response, testing for antibody titers is recommended before administration, and it is unlikely that members will be eligible to receive any type of subsequent gene therapy.⁸ Re-administration of delandistrogene moxeparvovec is not recommended.

Delandistrogene moxeparvovec was FDA approved through the accelerated approval pathway based on change in micro-dystrophin level.⁷ The clinical benefit has not been established, and available data from blinded, placebo-controlled trials show no overall motor function improvement compared to placebo.^{6,8} Continued approval is dependent on a subsequent phase 3, placebo-controlled confirmatory trial which was completed in late 2023. Full results from this trial have not yet been published.

Clinical Safety:

The FDA evaluated safety data from 85 people who received an infusion of delandistrogene moxeparvovec enrolled in 3 clinical studies.⁸ Of these patients, 73 received the FDA-approved dose.⁸ There were changes in the manufacturing process during clinical trials, and only 40 of these patients received delandistrogene moxeparvovec manufactured using the commercialized process.⁸ The infusion is administered in conjunction with an increased dose of corticosteroids (1 to 1.5 mg/kg/day prednisone equivalent) for 1 day prior to treatment and for at least 60 days post-treatment to decrease risk of an immune response.⁷ If liver function abnormalities occur, then the dose of corticosteroid should be increased (up to 2.5 mg/kg/day).⁷ After the 60 day period, the corticosteroid dose is tapered back to the patient’s usual maintenance dose over a periods of 2 weeks or longer.⁷

Baseline assessments prior to administration include genetic testing, tests for AAVrh74 binding antibodies, liver function tests, troponin, and platelets.⁷ Because of the need for prolonged immunosuppression, delandistrogene moxeparvovec is not recommended if there are signs or symptoms of infection and labeling recommends that patients be up-to-date with relevant immunizations at least 4 weeks prior to therapy.⁷

The most common adverse events observed in clinical trials were vomiting (61%), nausea (40%), acute liver injury (37%), pyrexia (24%), and thrombocytopenia (12%).⁸ Thrombocytopenia was generally transient and asymptomatic. Comparisons to placebo are shown in **Table 5**. Acute liver injury was defined as elevated liver function tests 2 to 3 times the upper limit of normal depending on the test. Patients with pre-existing liver impairment, acute or chronic liver disease or elevated GGT were excluded from clinical studies and may have an increased risk for liver injury.⁷ Treatment should be postponed until any acute liver injury is resolved. In clinical trials elevations in liver function tests typically occurred within 8 weeks and resolved with administration of systemic corticosteroids.

During clinical studies, 2 cases of immune-mediated myositis were documented after administration. The reaction was thought to be a T-cell based immune response to a specific region on the transgene.⁸ It occurred in patients with deletions involving exons 3-43 and exons 8-9 and was thought to be related to a lack of self-tolerance to this region of the transgene.⁸ Therefore, this therapy is contraindicated for anyone with deletions in exons 8 or 9 of the DMD gene.⁷ Labeling also includes warnings for patients with deletions in exons 1 to 17 and/or exons 59 to 71 who may also be at risk of severe immune-mediated myositis reactions. If symptoms of myositis occur (e.g., increased muscle pain, weakness, tenderness, dysphagia, dyspnea, or hypophonia), additional immunosuppressant therapy should be considered.⁷ Additional warnings in the labeling include acute serious myocarditis and elevated levels of troponin-I which have been observed after administration. Baseline and subsequent monitoring for cardiac injury is recommended.⁷

Table 5. Adverse events occurring in ≥10% of patients and more common than placebo during placebo-controlled studies⁷

	Delandistrogene moxeparvovec N=20 (%)	Placebo N=21 (%)
Vomiting	65%	33%
Nausea	35%	10%
Liver function test increases	25%	0%
Pyrexia	20%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
- 2) Disease progression
- 3) Quality of life
- 4) Mortality
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change from baseline to 48 weeks in NSAA score (motor function)
- 2) Change from baseline to 12 weeks in micro-dystrophin protein expression

Table 6. Pharmacology and Pharmacokinetic Properties.⁷

Parameter	
Mechanism of Action	Delandistrogene moxeparvovec is a recombinant gene therapy containing a non-replicating, adeno-associated virus capsid and single strand DNA expression cassette. The DNA expression cassette contains a promotor and transgene which are intended to express a shortened micro-dystrophin protein, replacing the lack of functional wild-type dystrophin protein for patients with DMD. The promoter region is intended to restrict gene expression to skeletal and cardiac muscle cells. The adeno-associated virus capsid transduction has been documented in skeletal muscle cells, cardiac cells and diaphragm muscle cells.
Oral Bioavailability	NA
Distribution and Protein Binding	Biodistribution was evaluated in animal studies. At 12 weeks following administration, vector DNA was detected in all major organs with highest levels in the liver, followed by the heart, adrenal glands, skeletal muscles and aorta. Micro-dystrophin protein expression was highest in cardiac tissue with lower levels in skeletal muscle, diaphragm and liver. With human testing in 2 clinical studies, vector genome exposure increased from baseline by 2.91 and 3.44 copies per nucleus in muscle biopsies at 12 weeks post-dose.
Elimination	Elimination in the urine and feces after systemic circulation and delivery of viral capsids to target tissues. C_{\max} was 0.0049×10^{13} copies/mL T_{\max} = 5.3 hours post-dose in serum, 13.5 days post-dose in the feces
Half-Life	Serum: about 12 hours; the majority of the drug is expected to be cleared from the serum by 1-week post-dose. Elimination half-life for urine: 40 hours Elimination half-life for feces: 55 hours Elimination half-life for saliva: 60 hours
Metabolism	Capsid is broken down through proteasomal degradation within target cells.

Abbreviations: C_{\max} = maximum concentration; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; NA = not applicable; T_{\max} = time to maximum concentration

Table 7. Comparative Evidence Table for Delandistrogene Moxeparvec.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability																		
Mendell, et al. 2023. ⁶ FDA Clinical Review Memo ⁸ NCT0376 9116 Phase 2, DB, crossover RCT	1. delandistrogene moxeparvec 1.33 × 10 ¹⁴ vg/kg IV one time dose 2. placebo Part 1: 48 weeks Corticosteroid were added or increased to 1mg/kg prednisone equivalent 1 day prior to treatment and continued for ≥ 60 days post-infusion. After 48 weeks, patients were crossed over to the other treatment group and followed for another 48 weeks.	Demographics: - Mean age 6.3 years (SD 1.2) - Daily corticosteroid: 49% - Time since corticosteroid was started: mean ~1 year (range 0.2 to 5 years) - Deflazacort: 33-35% - BMI: 17.2-17.9 kg/m ² <table><tr><th>Mean (SD)</th><th>Tx</th><th>PBO</th></tr><tr><td>NSAA</td><td>19.8 (3.3)</td><td>22.6 (3.3)</td></tr><tr><td>Time to rise (s)</td><td>5.10 (2.17)</td><td>3.56 (0.65)</td></tr><tr><td>4-stair climb (s)</td><td>3.69 (1.46)</td><td>3.10 (0.98)</td></tr><tr><td>100MRW (s)</td><td>61.04 (12.71)</td><td>53.86 (8.30)</td></tr><tr><td>TTRW 10 meters (s)</td><td>5.35 (1.14)</td><td>4.83 (0.72)</td></tr></table> Key Inclusion Criteria: - Age ≥4 to <8 years - Confirmed DMD gene mutation with frameshift (deletion, duplication or premature stop codon mutation) between exons 18 and 58 - Ambulatory and able to cooperate with motor testing - On stable oral corticosteroid ≥12 weeks - Creatine kinase >1,000 U/L - Percent predicted 100m run/walk time <95 th percentile Key Exclusion Criteria: - Cardiomyopathy or impaired CV function on echocardiogram - Other genetic disease - Other lab or physical findings that could affect safety, study completion or outcome assessment (such as gamma-glutamyl transferase ≥3x ULN,	Mean (SD)	Tx	PBO	NSAA	19.8 (3.3)	22.6 (3.3)	Time to rise (s)	5.10 (2.17)	3.56 (0.65)	4-stair climb (s)	3.69 (1.46)	3.10 (0.98)	100MRW (s)	61.04 (12.71)	53.86 (8.30)	TTRW 10 meters (s)	5.35 (1.14)	4.83 (0.72)	mITT: Patients who received treatment 1. 20 2. 21 Attrition: Part 1 1. 0 2. 0 Part 2 1. 0 2. 2	Primary Endpoint: Change in NSAA score at 48 weeks 1. 1.7 (SE 0.6) 2. 0.9 (SE 0.6) LSMD 0.8; (95% CI - 1.03 to 2.67); p=0.37 Change in dystrophin expression as 12 weeks (Western blot) - % of normal 1. 23.8% 2. 0.14% P<0.0001 Secondary Endpoints: Change from baseline to week 48 – negative values indicate improvement TTRW 10 m 1. 0.70 s (SD 1.16) 2. 0.01 s (SD 0.69) 100 m run/walk time 1. 8.67 s (SD 27.96) 2. 2.49 s (SD 7.52) 4-stair climb 1. 0.26 s (SD 1.35) 2. 0.03 s (SD 0.87) Mean time to stand from supine 1. -0.21 s (SD 1.13)	NA	Part 1 Treatment-related AE 1. 17 (85%) 2. 9 (43%) Serious AE 1. 3 (15%) 2. 2 (10%) Discontinuation due to AE 1. 0 (0%) 2. 0 (0%) Rhabdomyolysis 1. 2 (10%) 2. 1 (5%) Liver injury 1. 1 (5%) 2. 0 (0%)	NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> High. Adequate methods for randomization and allocation concealment via IVWRS stratified by age. Patients randomized to treatment in part 1 had worse motor function scores than placebo. Disparities between groups were more apparent for patients 6-7 years of age. <u>Performance Bias:</u> Unclear. Double blinded up to 48 weeks, but method of blinding was not reported. <u>Detection Bias:</u> Unclear. Double blinded but method of blinding was not reported. <u>Attrition Bias:</u> Low. Only 1 patient with missing outcome data for the primary endpoint at 48 weeks. <u>Reporting Bias:</u> High. Post-hoc analyses were conducted for subgroups based on age without pre-specified statistical testing to control for multiplicity and type 1 error. Statistical analyses for secondary outcomes were not reported, but did not have apparent differences between groups. <u>Other Bias:</u> Unclear. Part 2 data after cross over treatment were compared using propensity-match to external controls which increases risk of bias. Controls were only matched based on age, NSAA scores, time to rise, time to walk/run 10 meters, and corticosteroid dose. This method does not control for unknown confounding factors. Study was funded by Sarepta, 6 of study authors were employees of Sarepta and all authors were involved in study design, data analysis, interpretation, writing and manuscript preparation. Applicability: <u>Patient:</u> Evidence is most applicable to patients with a confirmed DMD frameshift mutation and less than 8 years of age. Patients were ambulatory, but had an abnormal time to run/walk 100 m for their age. <u>Intervention:</u> Only 8 patients received a dose comparable the commercialized product. Patients were required to be on a stable dose of corticosteroids which is a first-line treatment option for DMD.
Mean (SD)	Tx	PBO																								
NSAA	19.8 (3.3)	22.6 (3.3)																								
Time to rise (s)	5.10 (2.17)	3.56 (0.65)																								
4-stair climb (s)	3.69 (1.46)	3.10 (0.98)																								
100MRW (s)	61.04 (12.71)	53.86 (8.30)																								
TTRW 10 meters (s)	5.35 (1.14)	4.83 (0.72)																								

		bilirubin ≥ 3 mg/dL; creatinine ≥ 1.8 mg/dL; hemoglobin < 8 or > 18 g/dL; WBC $> 18,500/\text{mm}^3$ - Concomitant disease (including HIV, hepatitis B or C, autoimmune disease, cognitive impairment that could confound motor tests) - Severe infection within 4 weeks - rAAVrh74 antibody titers $> 1:400$ (e.g., not elevated)		2. 0.44 s (SD 0.91)				<u>Comparator:</u> Placebo is appropriate to determine efficacy. Even though trial remained blinded, after the crossover at 48 weeks, all patients had received treatment, making the study essentially non-controlled. The FDA relied primarily on placebo-controlled data in the first 48 weeks to evaluate efficacy. <u>Outcomes:</u> Outcomes were appropriate to evaluate motor function. Performance on motor function tests is highly dependent on motivating factors and method of administration. There was no correlation between micro-dystrophin expression and functional motor outcomes. <u>Setting:</u> 2 sites in the United States (Ohio and California) from 2018 to 2020.
<u>Abbreviations:</u> 100MRW = 100 meter run/walk time; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double blind; dL = deciliter; DMD = Duchenne muscular dystrophy; HIV = human immunodeficiency virus; ITT = intention to treat; IVWRS = interactive voice/web response system; LSDM = least square mean difference; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NSAA = North star ambulatory assessment; PBO = placebo; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TTRW = time to run/walk; Tx = delandistrogene moxeparvovec; ULN = upper limit of normal; WBC = white blood cell								

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>
casimersen	AMONDYS-45	VIAL
deflazacort	EMFLAZA	ORAL SUSP
deflazacort	EMFLAZA	TABLET
eteplirsen	EXONDYS-51	VIAL
viltolarsen	VILTEPSO	VIAL
golodirsen	VYONDYS-53	VIAL

Appendix 2: Abstracts of Comparative Clinical Trials

Guglieri M, Bushby K, McDermott MP, et al. Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. *Jama*. 2022;327(15):1456-1468.

Importance: Corticosteroids improve strength and function in boys with Duchenne muscular dystrophy. However, there is uncertainty regarding the optimum regimen and dosage.

Objective: To compare efficacy and adverse effects of the 3 most frequently prescribed corticosteroid regimens in boys with Duchenne muscular dystrophy.

Design, Setting, and Participants: Double-blind, parallel-group randomized clinical trial including 196 boys aged 4 to 7 years with Duchenne muscular dystrophy who had not previously been treated with corticosteroids; enrollment occurred between January 30, 2013, and September 17, 2016, at 32 clinic sites in 5 countries. The boys were assessed for 3 years (last participant visit on October 16, 2019)., Interventions: Participants were randomized to daily prednisone (0.75 mg/kg) (n = 65), daily deflazacort (0.90 mg/kg) (n = 65), or intermittent prednisone (0.75 mg/kg for 10 days on and then 10 days off) (n = 66).

Main Outcomes and Measures: The global primary outcome comprised 3 end points: rise from the floor velocity (in rise/seconds), forced vital capacity (in liters), and participant or parent global satisfaction with treatment measured by the Treatment Satisfaction Questionnaire for Medication (TSQM; score range, 0 to 100), each averaged across all study visits after baseline. Pairwise group comparisons used a Bonferroni-adjusted significance level of .017.

Results: Among the 196 boys randomized (mean age, 5.8 years [SD, 1.0 years]), 164 (84%) completed the trial. Both daily prednisone and daily deflazacort were more effective than intermittent prednisone for the primary outcome ($P < .001$ for daily prednisone vs intermittent prednisone using a global test; $P = .017$ for daily deflazacort vs intermittent prednisone using a global test) and the daily regimens did not differ significantly ($P = .38$ for daily prednisone vs daily deflazacort using a global test). The between-group differences were principally attributable to rise from the floor velocity (0.06 rise/s [98.3% CI, 0.03 to 0.08 rise/s] for daily prednisone vs intermittent prednisone [$P = .003$]; 0.06 rise/s [98.3% CI, 0.03 to 0.09 rise/s] for daily deflazacort vs intermittent prednisone [$P = .017$]; and -0.004 rise/s [98.3% CI, -0.03 to 0.02 rise/s] for daily prednisone vs daily deflazacort [$P = .75$]). The pairwise comparisons for forced vital capacity and TSQM global satisfaction subscale score were not statistically significant. The most common adverse events were abnormal behavior (22 [34%] in the daily prednisone group, 25 [38%] in the daily deflazacort group, and 24 [36%] in the intermittent prednisone group), upper respiratory tract infection (24 [37%], 19 [29%], and 24 [36%], respectively), and vomiting (19 [29%], 17 [26%], and 15 [23%]).

Conclusions and Relevance: Among patients with Duchenne muscular dystrophy, treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens. The findings support the use of a daily corticosteroid regimen over the intermittent prednisone regimen tested in this study as initial treatment for boys with Duchenne muscular dystrophy. Trial Registration: ClinicalTrials.gov Identifier: NCT01603407.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 20, 2023

1	vamorolone.mp.	30
2	delandistrogene moxeparvovec.mp.	7
3	delandistrogene moxeparvovec-rokl.mp.	1
4	SRP-9001.mp.	4
5	eteplirsen.mp.	171
6	casimersen.mp.	20
7	viltolarsen.mp.	44
8	golodirsen.mp.	49
9	deflazacort.mp.	641
10	exp Muscular Dystrophy, Duchenne/	7226
11	9 and 10	137
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11	363
13	limit 12 to yr="2021"	26
14	limit 12 to yr="2022 -Current"	71
15	limit 14 to (english language and humans)	50
16	limit 15 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	14

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AGAMREE® safely and effectively. See full prescribing information for AGAMREE.

AGAMREE (vamorolone) oral suspension

Initial U.S. Approval: 2023

INDICATIONS AND USAGE

AGAMREE is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 6 mg/kg taken orally once daily preferably with a meal, up to a maximum daily dosage of 300 mg for patients weighing more than 50 kg. (2.2)
- In patients with mild to moderate hepatic impairment, the recommended dosage is 2 mg/kg taken orally once daily preferably with a meal, up to a maximum daily dosage of 100 mg for patients weighing more than 50 kg. (2.3)
- Decrease dosage gradually when administered for more than one week. (2.7)

DOSAGE FORMS AND STRENGTHS

Oral Suspension: 40 mg/mL (3)

CONTRAINDICATIONS

Hypersensitivity to vamorolone or any of the inactive ingredients in AGAMREE (4)

WARNINGS AND PRECAUTIONS

- *Alterations in Endocrine Function:* Hypothalamic-pituitary-adrenal axis suppression, cushingoid features, and hyperglycemia can occur. Monitor patients for these conditions with chronic use of AGAMREE. (2.7, 5.1)
- *Immunosuppression and Increased Risk of Infection:* Increased risk of new infections, exacerbation, dissemination, or reactivation of latent infections,

which can be severe and at times fatal; signs and symptoms of infections may be masked. (5.2)

- *Alterations in Cardiovascular/Renal Function:* Monitor for elevated blood pressure and monitor sodium and potassium levels in patients chronically treated with AGAMREE. (5.3)
- *Gastrointestinal Perforation:* Increased risk in patients with certain GI disorders; signs and symptoms may be masked. (5.4)
- *Behavioral and Mood Disturbances:* May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. (5.5)
- *Effects on Bones:* Monitor for decreases in bone mineral density with chronic use of AGAMREE. (5.6)
- *Ophthalmic Effects:* May include cataracts, infections, and glaucoma; monitor intraocular pressure in patients chronically treated with AGAMREE. (5.7)
- *Vaccination:* Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting AGAMREE. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (>10% for AGAMREE and greater than placebo) are cushingoid features, psychiatric disorders, vomiting, weight increased, and vitamin D deficiency. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Santhera Pharmaceuticals (Switzerland) Ltd. at 1-844-347-3277 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Strong CYP3A4 inhibitors:* The maximum recommended daily dose is 4 mg/kg up to a maximum daily dosage of 200 mg for patients weighing more than 50 kg. (2.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2023

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELEVIDYS safely and effectively. See full prescribing information for ELEVIDYS.

ELEVIDYS (delandistrogene moxeparvovec-rokl) suspension, for intravenous infusion

Initial U.S. Approval: YYYY

INDICATIONS AND USAGE

ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. This indication is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin in skeletal muscle observed in patients treated with ELEVIDYS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1, 12, 14)

DOSAGE AND ADMINISTRATION

ELEVIDYS is for single-dose intravenous infusion only.

- Select patients for treatment with ELEVIDYS with anti-AAVrh74 total binding antibody titers <1:400. (2.1)
- Recommended dosage: 1.33×10^{14} vector genomes (vg) per kg of body weight. (2.2)
- Postpone in patients with concurrent infections until the infection has resolved. (2.2)
- Assess liver function, platelet counts and troponin-I before ELEVIDYS infusion. (2)
- One day prior to infusion, initiate a corticosteroid regimen for a minimum of 60 days. Recommend modifying corticosteroid dose for patients with liver function abnormalities. (2.2)
- Administer as an intravenous infusion over 1-2 hours. Infuse at a rate of less than 10 mL/kg/hour. (2.4)

DOSAGE FORMS AND STRENGTHS

- ELEVIDYS is a suspension for intravenous infusion with a nominal concentration of 1.33×10^{13} vg/mL. (3)

- ELEVIDYS is provided in a customized kit containing ten to seventy 10 mL single-dose vials, with each kit constituting a dosage unit based on the patient's body weight. (3)

CONTRAINDICATIONS

- ELEVIDYS is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene. (4)

WARNINGS AND PRECAUTIONS

- **Acute Serious Liver Injury:** Acute serious liver injury has been observed. Monitor liver function before ELEVIDYS infusion, and weekly for the first 3 months after ELEVIDYS infusion. Continue monitoring until results are unremarkable. If acute serious liver injury is suspected, a consultation with a specialist is recommended. (5.1)
- **Immune-mediated Myositis:** Patients with deletions in the *DMD* gene in exons 1 to 17 and /or exons 59 to 71 may be at risk for severe immune-mediated myositis reaction. Consider additional immunomodulatory treatment (immunosuppressants [e.g., calcineurin-inhibitor] in addition to corticosteroids) if symptoms of myositis occur (e.g., unexplained increased muscle pain, tenderness, or weakness). (5.2)
- **Myocarditis:** Myocarditis and troponin-I elevations have been observed. Monitor troponin-I before ELEVIDYS infusion, and weekly for the first month after ELEVIDYS infusion. (5.3)
- **Pre-existing Immunity against AAVrh74:** Perform baseline testing for presence of anti-AAVrh74 total binding antibodies prior to ELEVIDYS administration. (5.4)

ADVERSE REACTIONS

Most common adverse reactions across studies (incidence $\geq 5\%$) were vomiting and nausea, liver function test increased, pyrexia, and thrombocytopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc., at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: X/XXXX

Appendix 5: Key Inclusion Criteria

Population	People with Duchenne Muscular Dystrophy
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1, placebo or standard of care
Outcomes	Symptoms, function, quality of life, morbidity, disease progression, mortality
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Duchenne Muscular Dystrophy

Goal(s):

- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of targeted oligonucleotides for exon skipping to patients with Duchenne Muscular Dystrophy.
- Limit use of non-preferred corticosteroids to patients with contraindications or serious intolerance to preferred oral corticosteroids.

Length of Authorization:

- 6-12 months (criteria-specific)

Requires PA:

- Targeted therapies for exon skipping (see Table 1; pharmacy or physician administered claims)
- Non-preferred corticosteroids for Duchenne muscular dystrophy (e.g., deflazacort, etc)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
casimersen (Amondys 45®)	Duchenne muscular dystrophy with mutations amenable to exon 45 skipping	Deletion of exons 44, 46, 46 to 47, 46 to 48, 46 to 49, 46 to 51, 46 to 53, 46 to 55, or 46 to 57
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58
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Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of Duchenne Muscular Dystrophy?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for a corticosteroid?	Yes: Go to #4	No: Go to #7
4. Is the patient ≥ 2 years of age?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least one dose of measles, mumps, rubella, and varicella.	Yes: Go to #6 Document physician attestation of immunization history.	No: Pass to RPh. Deny; medical appropriateness.
6. Does the patient have a documented contraindication or intolerance to a preferred corticosteroid, such as oral prednisone, that is not expected to crossover to the requested therapy? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	Yes: Approve for up to 12 months. Document contraindication or intolerance reaction.	No: Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.

Approval Criteria		
7. Is the request for continuation of treatment previously approved by FFS?	Yes: Go to Renewal Criteria	No: Go to #8
8. Is the request for an FDA-approved indication (Table 1)?	Yes: Go to #9 Document genetic testing.	No: Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	Yes: Go to #10	No: Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #11
11. Has the provider assessed baseline renal function as recommended in the FDA label? Recommended monitoring includes serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	Yes: Go to #12	No: Pass to RPh. Deny; medical appropriateness.
12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	Yes: Go to #13	No: Pass to RPh. Deny; medical appropriateness.
13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	Yes: Document baseline functional assessment and approve for up to 6 months	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	Yes: Go to #2	No: Go to #3

Renewal Criteria		
<p>2. Has the provider assessed renal function?</p> <p>Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatinine ratio every 3 months.</p>	<p>Yes: Go to #3</p>	<p>No: Pass to RPh, Deny; medical appropriateness.</p>
<p>3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?</p>	<p>Yes: Go to #4</p> <p>Document functional status and provider attestation.</p>	<p>No: Pass to RPh, Deny; medical appropriateness.</p>
<p>4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?</p>	<p>Yes: Go to #5</p>	<p>No: Approve for up to 6 months</p>
<p>5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?</p>	<p>Yes: Approve for up to 6 months</p> <p>Document provider attestation</p>	<p>No: Pass to RPh, Deny; medical appropriateness.</p>

P&T/DUR Review: 2/24; 8/21 (SS); 2/21; 6/20; 09/19; 11/17; 07/17
Implementation: 9/1/21; 3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17

Delandistrogene moxeparvovec

Goal(s):

- Restrict use of this gene therapy to patients with the FDA-labeled indication.

Length of Authorization:

- 1 lifetime dose

Requires PA:

- Delandistrogene moxeparvovec (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of genetically-confirmed Duchenne Muscular Dystrophy?	Yes: Go to #3 Results of genetic testing are required for approval.	No: Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the medication prescribed by a neuromuscular specialist?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness.
4. Is the patient 4 or 5 years of age?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Is the patient ambulatory (e.g., able to complete a 6 minute walk test or equivalent assessment)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Does the patient have deletions of exon 8 or 9?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #7
7. For patients with deletions of exons 1 to 17 or exons 59 to 71, is there documentation that the provider and patient have discussed potential risks of treatment? Note: these populations were excluded from clinical studies and may have increased risk for severe immune-mediated myositis reactions.	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
<p>8. Has baseline testing been completed and is within normal limits?</p> <p>Recommended baseline testing includes testing for anti-AAVrh74 antibodies (by ELISA), troponin-I, platelets, and liver function tests.</p>	<p>Yes: Go to #9</p> <p>For any testing that is not within normal limits, refer to medical director for review. Liver function tests should be <3x the upper limit of normal.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>9. Has the patient received, or have contraindications to, all routine immunizations recommended for their age?</p> <p>Note: Routine vaccinations for patients at least 4 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, COVID-19, and at least 2 doses of measles, mumps, rubella, and varicella.</p>	<p>Yes: Go to #10</p> <p>Document provider attestation of immunization history.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>10. Is the patient able to tolerate an elevated dose of prednisone for at least 60 days and complete necessary ongoing monitoring?</p>	<p>Yes: Go to #11</p> <p>Document provider attestation.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>11. Has the patient received a prior dose of an adeno-based gene therapy?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p>	<p>No: Approve single infusion (max 1 dose per lifetime)</p>

P&T/DUR Review: 2/24 (SS)
Implementation: 4/1/24