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# Drug Class Update with New Drug Evaluation: Duchenne Muscular Dystrophy

**Date of Review:** October 2024

**Date of Last Review:** February 2024
**Dates of Literature Search:** 1/1/2023-7/26/2024
**Brand Name (Manufacturer):** Duvyzat (Italfarmaco Therapeutics)
**Dossier Received:** No

**Generic Name:** givinostat

**Current Status of PDL Class:**
See **Appendix 1**.

**Purpose for Class Update:**
The purpose of this update is to evaluate efficacy and safety of givinostat and evaluate new evidence pertaining to drugs for Duchenne muscular dystrophy (DMD) published since the last class review.

**Plain Language Summary:**
- People who have Duchenne muscular dystrophy (DMD) slowly lose muscle strength and ability to walk over time.
- The American Academy of Neurology recommends steroids for people with DMD because studies show that they extend the time people are able to walk and delay the need for a wheelchair. Studies do not show that one steroid improves muscle function better than another.
- In controlled studies, other medicines that the Food and Drug Administration (FDA) has approved for DMD have not shown that they improve symptoms or change the course of the disease.
- The FDA recently approved a new medicine called a gene therapy for people with DMD. The name of this medicine is delandistrogene moxeparvovec. The goal of this medicine is to delay worsening muscle symptoms for people with DMD. However, two studies have shown that people who took this medicine had similar muscle function compared to those who did not get the treatment after about 1 year.
- A new medicine called givinostat was also approved by the FDA. People taking givinostat may have had slower decline in motor function compared to people taking placebo (or sugar pill), but the amount of benefit is very uncertain. Common side effects of givinostat include diarrhea and nausea. Givinostat can decrease platelets (a type of blood cell that helps stop bleeding in cuts) and increase triglycerides (a type of fat). Routine blood tests are recommended to prevent complications from these side effects.
- 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 givinostat to this policy.

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**Research Questions:**

1. What is the comparative efficacy or effectiveness of therapies for 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 givinostat for the treatment of people with DMD?
4. 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:**

- Since the last class update, there is no new direct comparative evidence published for drug therapies in people with DMD. The FDA has approved an expanded indication for the gene therapy, delandistrogene moxeparvovec, and a new histone deacetylase (HDAC) inhibitor called givinostat for people with DMD. The expanded indication for delandistrogene moxeparvovec included people with DMD who are non-ambulatory and over 5 years of age.[1]
- There is insufficient evidence to evaluate impact of givinostat on motor function outcomes in patients with DMD. Available evidence is limited by risk for performance selection and attrition bias, imprecision, and evaluation in people who are likely to have gradual disease progression. When a mixed model for repeated measures was used to account for missing data, there was no difference between givinostat and placebo in the time to climb 4 stairs (mean difference [MD] -1.64 seconds, standard error [SE] 0.94, p=0.083).[2] Secondary motor outcomes including NSAA scores did not achieve statistical significance based on the pre-specified testing plan.[2,3] However, based on a positive correlation between exposure and NSAA scores during the phase 3 clinical trial, pharmacodynamic data demonstrating less fat infiltration in muscle cells, and a consistent direction of effect on motor function in an uncontrolled, observational trial, the FDA recommended approval of givinostat based on the totality of the evidence.[2]
- Common adverse events associated with givinostat include gastrointestinal disturbances (e.g., diarrhea, nausea, vomiting, abdominal pain, and decreased appetite), thrombocytopenia, increased triglycerides, pyrexia, rash, arthralgia, and fatigue.[4] Side effects were generally dose-related, and 42% of people had dose modifications due to adverse events compared to 8% of people treated with placebo.[2]
- Two RCTs in patients treated with delandistrogene moxeparvovec have shown no difference in motor function compared to placebo after 48 and 52 weeks (low quality evidence).[5,6] In the initial placebo-controlled RCT used for accelerated approval, there was no statistical difference compared to placebo in the NSAA score at 48 weeks (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).[5] Secondary timed motor function tests were also no different between groups.[5] The unpublished, confirmatory phase 3 RCT showed no difference in the NSAA score compared to placebo (MD 0.65 points; 95% CI not reported, p=0.2441).[6] Results were not reported for all secondary motor outcomes, and when reported, had mean differences that were generally small. For secondary outcomes, the lack of a pre-specified analysis plan to control for type 1 error increases risk for false positive results.[6] There was insufficient data from subgroup analyses to identify people who are likely to have the most benefit from treatment. Despite these results, the delandistrogene moxeparvovec received an expanded indication in all patients with DMD who are at least 4 years of age.

**Recommendations:**

- Update prior authorization criteria to incorporate the expanded indication for delandistrogene moxeparvovec and givinostat (**Appendix 5**).
- No PDL changes recommended based on comparative evidence.
- After review of costs in executive session, EMFLAZA (deflazacort) tablets (brand only) were made preferred with clinical PA.

**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 2024.

- Corticosteroids are recommended as a first-line treatment for patients with DMD. Evidence from direct comparative RCTs shows no difference in efficacy between corticosteroids.[7,8] A RCT evaluating daily deflazacort or prednisone in people with DMD demonstrated comparable muscle and pulmonary function after 3 years.[7] Comparative data for vamorolone and prednisone is limited to 6 months.[8] Daily corticosteroid regimens (deflazacort or prednisone) were better at preserving muscle function than intermittent prednisone use.[7]
- Prior reviews have identified insufficient evidence to evaluate differences in safety between corticosteroids for DMD.[9,10] Deflazacort may be associated with less weight gain but more vision problems than prednisone.[7] There is insufficient evidence to evaluate whether vamorolone and prednisone have different effects on risk of fracture, growth, or development in people with DMD.[11]
- 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.
- 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.[5] There was no statistical difference in the 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% confidence interval [CI] -1.03 to 2.67; p=0.37).[5] Secondary timed motor function tests were also no different between groups.[5] FDA approval was based on a post-hoc, subgroup analysis in people 4-5 years of age.
- Prior authorization (PA) is currently required for deflazacort, vamorolone, and all target therapies for DMD to ensure medically appropriate use (see **Appendix 5**). 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. Duchenne muscular dystrophy 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.[12] 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,[12,13] and the estimated incidence of new DMD patients is 1 in approximately 5,000 male births.[14] 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.[12] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival have been documented over time.[15] Improved survival has been attributed to improvements in supportive care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[15] 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.[15] 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.[15]

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.[12] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[12] Available drug treatments include corticosteroids and targeted gene modification or exon-skipping therapies. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids 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.[12,16] Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[12] 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.[7] Available evidence from direct comparative RCTs does not show any difference in efficacy between different corticosteroids for DMD.[7,8] However, daily corticosteroids may preserve muscle function better than intermittently dosed corticosteroids.[7]

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.[17] While exon-skipping therapies have shown a slight increase in dystrophin, the impact of these therapies on clinical outcomes had not been demonstrated inRCTs.[18,19] 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.[20] 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.[25] 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.[25] 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.[26] Experts suggest that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[26] 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.[26,27] In patients with Becker muscular dystrophy, a less severe form of muscular dystrophy, dystrophin protein levels are on average 80% of normal.[26] An FDA analysis evaluating the change in 6MWT per year and dystrophin level changes associated with golodirsen failed to demonstrate a positive correlation, indicating that small increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[20]

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 assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the NSAA is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34).[28,29] 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 (MCID) 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.[25] 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.[25] However, there was significant heterogeneity among patients. In people with DMD, 25% of people had a NSAA score less than or equal to 5 points by age 10.[25] NSAA scores had declined to less than 5 points in 35% of people by age 12 and in 21% of people by age 14.[25] About 19% of patients had NSAA scores that remained greater than 5 points beyond 15 years of age.[25]

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.[30] 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 MCID for ambulatory patients with DMD.[31] 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.[31] 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).[31] 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.[31] 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.[31] 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.[24,32,33] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[30] 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.[29] 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 and method of administration.[26]

**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 2**, 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, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) 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:**
No high quality systematic reviews have been published since the last class update.

**New Guidelines:**
No high quality guidelines have been published since the last class update.

**New Formulations or Indications:**
In June 2024, delandistrogene moxeparvovec received an expanded indication for non-ambulatory people with DMD and for people over 5 years of age. Delandistrogene moxeparvovec is a gene therapy that was previously approved under the accelerated approval pathway for ambulatory patients with DMD who were 4 to 5 years of age. Initial approval was based on a placebo-controlled trial evaluating dystrophin expression and motor function in ambulatory patients 4 to 7 years of age with DMD over 48 weeks.[5] There was no statistical difference in the 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).[5] Secondary outcomes evaluating timed motor function tests were also no different between groups.[5] FDA initial approval was based on a post-hoc, subgroup analysis in people 4 to 5 years of age.

The expanded approval for patients over 5 years of age was based on a confirmatory, double blind, placebo-controlled, phase 3 trial involving 125 ambulatory participants 4 to 7 years of age.[6] The trial was unpublished as of July 2024. The primary outcome was change in NSAA score after 52 weeks. Other secondary motor outcomes included the number of NSAA items gained, time to rise from a supine position, 100 meter walk/run time, time to climb 4 stairs, 10 meter run/walk time, the stride velocity 95$^{th}$ centile (SV95C) ambulatory assessment, and patient/caregiver reported mobility and upper extremity function assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS).[6] The PROMIS upper extremity assessment evaluates ability to complete daily tasks using the upper extremities.[34] Each question is rated on a 1-5 scale ranging from no difficulty completing the task to unable to complete the task.[34] The SV95C is a wearable device that is intended to measure peak ambulatory ability by identifying the velocity of the top 5% most rapid strides taken by the wearer in a real world setting.[35]

Participants were required to have an NSAA score between 16 and 29 at baseline, a time to rise from the floor of less than 5 seconds, and be prescribed a stable dose of corticosteroids.[6] The average age of enrolled participants was 6 years and most participants identified as white (78%) or Asian (13%). The average baseline time to rise from the floor was about 3.5 seconds, the time to climb 4 stairs was 3.2 seconds, and the average NSAA score was 23 points. Participants were excluded if they had cardiomyopathy or a left ventricular ejection fraction (LVEF) less than 40%.[6] Patients with pre-existing cardiac disease may have increased risk for adverse events related to myocarditis.[1]

The study was powered to detect differences in NSAA scores from baseline, but not powered to detect differences in secondary outcomes. Missing data was handled using mixed method for repeated measures.[6] There was no pre-specified multiplicity adjustment testing plan to control for type 1 error. At 52 weeks, NSAA scores had improved by an average of 2.57 (SE 0.39) points with delandistrogene moxeparvovec compared to a 1.92 (SE 0.39) point improvement with placebo (MD 0.65 points; 95% CI not reported, p=0.2441).[6] Secondary outcomes were not reported in all cases, and when reported, had mean differences that were generally small. The FDA noted an increased risk for false positive results based on lack of a pre-specified analysis plan to control for type 1 error.[6] Results of secondary outcomes are reported as follows:[6]

- NSAA items gained: not reported
- Time to Rise (seconds): LSMD -0.64 ± SE 0.21 (95% CI -1.06 to -0.23)
- Time to Ascend 4 Steps (seconds): LSMD -0.36 ± SE 0.18 (95% CI -0.71 to -0.01)
- 10-Meter Walk/Run (seconds): LSMD -0.42 ± SE 0.15 (95% CI -0.71 to -0.13)
- 100-Meter Walk/Run (seconds): LSMD -3.29 ± SE 2.52 (95% CI -8.28 to 1.70)
- Stride velocity 95$^{th}$ centile (SV95C) ambulatory assessment measured via wearable device: not reported
- Mobility and upper extremity function on the PROMIS score: not reported

Subgroup analysis for outcomes based on age demonstrated similar results as earlier trials. Younger patients (4-5 years of age) had gains in NSAA which is consistent with the natural disease course.[6] Older patients (6-7 years of age) in both the placebo and delandistrogene moxeparvovec groups had smaller changes in NSAA scores.[6]

Adverse events observed in the phase 3 confirmatory trial were similar to earlier studies of delandistrogene moxeparvovec. Common adverse events included vomiting, decreased appetite, and increases in glutamate dehydrogenase.[6] Acute liver injury occurred in 41% of patients administered delandistrogene moxeparvovec compared to 8% of patient who received placebo (predominately with mild or moderate symptoms that resolved with an increased corticosteroid dose).[6] Serious adverse events occurred more commonly in people treated with delandistrogene moxeparvovec compared to placebo (22% vs. 8%).[6] Serious adverse events included myocarditis, hepatobiliary disorders including liver injury, nausea and vomiting, and rhabdomyolysis.[6]

Expanded approval for non-ambulatory patients was based on dystrophin levels in a non-controlled, open-label, cohort study involving 8 patients who were non-ambulatory.[1] The open-label design and lack of control group increases risk of bias and limits confidence in motor function results with delandistrogene moxeparvovec in this population. Post-marketing requirements include a randomized controlled trial to confirm the clinical benefit of delandistrogene moxeparvovec in people with DMD who are non-ambulatory.

**New FDA Safety Alerts:**

**Table 1. Description of New FDA Safety Alerts**

| Generic Name | Brand Name | Month / Year of Change | Location of Change | Addition or Change and Mitigation Principles (if applicable) |
|---|---|---|---|---|
| Deflazacort[36]<br>Vamorolone[37] | Emflaza®<br>Agamree® | 6/2024 | Warnings/Precautions | Risk for immunosuppression and infection was updated in FDA labeling to include tuberculosis reactivation in patients with latent infection, hepatitis B reactivation, and precautions for use in patients with concomitant fungal and parasitic infections. |
| Golodirsen[38] | Vyondys 53® | 6/2024 | Contraindications | Labeling updated to include contraindications in people with serious hypersensitivity reactions to golodirsen. Hypersensitivity reactions including anaphylaxis have occurred in postmarketing studies. |

**Randomized Controlled Trials:**

A total of 54 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). No randomized comparative clinical trials were identified.

**NEW DRUG EVALUATION:**

See **Appendix 3** 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:**

Givinostat is a histone deacetylase (HDAC) inhibitor FDA approved for treatment of DMD in patients at least 6 years of age. Histone deacetylase affects protein expression and regulation of follistatin. Inhibition of histone deacetylase in DMD is thought to increase muscle generation and reduce the fraction of healthy muscle cells that are replaced with fatty tissue or fibrosis. Approval was based primarily on a double-blind, placebo-controlled phase 3 study evaluating efficacy and safety in 179 patients over 18 months.[3,4] The FDA also considered supplementary data from an observational, open-label extension study which compared efficacy of givinostat to natural history data in matched patients.[2]

The phase 3 trial enrolled males with genetically confirmed DMD who were ambulatory and able to complete 2 separate 4-stair climb tests in under 8 minutes and had a time to rise from the floor in 3 to 10 seconds (average was 3.4 seconds).[3] The average patient age was 9.8 years at baseline, and all patients were prescribed concomitant corticosteroids. People were excluded if they were prescribed other targeted treatments for DMD (including gene therapy or exon skipping therapy), had had loss of ankle plantar flexion greater than or equal to 30$^{o}$, heart failure, or LVEF less than 50%.[3] The pre-specified analysis plan was designed to evaluate outcomes only in a subset of patients with a baseline vastus lateralis fat fraction between 5% and 30%.[3] This was intended to identify people who were at risk of motor function decline but not at risk for sudden loss of ambulation. The primary endpoint was time to climb 4 stairs. Secondary clinical endpoints included a variety of other motor function assessments. The amount of fat infiltration in the vastus lateralis muscle of the thigh was also evaluated at 72 weeks, and was used to confirm the pharmacodynamics of givinostat. Increases in the vastus lateralis fat fraction have been correlated with disease progression and functional decline in patients with DMD.[2]

The study used adequate randomization and blinding methods. However, incidence of adverse effects associated with givinostat may have led to functional unblinding of treatment groups which increases risk of performance bias, particularly for motor function tests where outcomes are highly dependent on motivating factors and method of administration. Baseline characteristics were generally balanced between groups but people randomized to givinostat were more likely to have duplication mutations and less likely to have point mutations.[3] The proportion of people on daily compared to intermittent corticosteroids was also higher with givinostat (85% vs. 80%).[2] Daily corticosteroids have been correlated with improved functional status in direct comparative trials compared to intermittently dosed corticosteroids. Deflazacort was the most common corticosteroid prescribed (81% with givinostat vs. 74% with placebo).[3]

The primary analysis was conducted in people with a vastus lateralis fat fraction of 5 to 30%, a criteria that was intended to identify people at risk for gradual motor function decline.[3] People treated with givinostat over 72 weeks had a mean decline of 1.25 seconds (95% CI 0.31 to 2.18) in the time required to climb 4 stairs. Comparatively, the time to climb 4 stairs declined by an average of 3.03 seconds (95% CI 1.67 to 4.39) in people treated with placebo (mean difference -1.78; 95% CI -3.46 to -0.11).[3] The proportion of people who discontinued the study was overall small. However, 12 patients (10% of participants) had missing outcome measures at 72 weeks that were missing for reasons unrelated to their ability to perform the functional test.[2] Missing values were imputed based on a single-value average from other participants in the group for that timepoint. This method ignores the potential uncertainty of imputed values and may create an artificially narrow measure of variance.[2] When reanalyzed based on a mixed method repeated measures model including all observed data as recommended in regulatory guidance from the FDA, results showed similar magnitude of effect, but wider variance, and the primary endpoint was no longer statistically different from placebo (MD -1.64 s, SE 0.94, p=0.083).[2]

Secondary motor function outcomes nominally favored givinostat compared to placebo, and NSAA scores were less sensitive to missing data.[2] However, based on the pre-specified statistical analysis plan to control for multiplicity and type 1 error (i.e., rate of false positive results), secondary outcomes did not achieve statistical significance compared to placebo.[3] Secondary outcomes included NSAA score, cumulative loss of function for items on the NSAA scale, time to rise from the floor, the distance walked in 6 minutes, knee extension strength, and elbow flexion strength. Results of each outcome are reported in **Table 4.**
The FDA conducted several subgroup analyses. None of the subgroup analyses demonstrated statistically significant differences compared to placebo, but there was a general trend for improved motor function outcomes in younger patients. There was also a similar magnitude of effect people with a vastus lateralis fat fraction less than 5% or greater than 30% (mean difference from placebo in the timed 4 stair climb -2.78 seconds; SE 2.60, p = 0.29).[2] However, the study was not powered to detect difference from placebo for subgroups, and subgroup analyses should be interpreted with caution. A wide range of doses were evaluated in clinical trials, and there was a positive correlation between cumulative exposure to givinostat and improved NSAA scores at 12 and 18 months.[2] The correlation between exposure and other motor function outcomes was not as strong and inconsistent depending on the outcome and timepoint evaluated.[2]

Overall, there is insufficient evidence to evaluate givinostat on motor function outcomes in patients with DMD. Available evidence is limited by risk for performance and selection bias and imprecision. Analysis of people with a vastus lateralis fat fraction between 5 and 30% limits applicability to people who are likely to have gradual disease progression. There was a trend toward improved motor function outcomes with givinostat compared to placebo. However, upon rigorous statistical testing, there was no difference compared to placebo in the time to climb 4 stairs. Secondary motor function outcomes did not differentiate from placebo based on the pre-specified statistical analysis plan. However, the study was not powered to detect differences in secondary outcomes, and planned enrollment was reduced from 192 to 102 following an interim efficacy analysis.[2] There is no evidence evaluating effect of givinostat on lung or cardiac function in patients with DMD. Because the primary analysis included people who were at risk for gradual disease progression, it is unclear if people who have more severe or less severe disease would experience similar outcomes. Givinostat has been evaluated in phase 2 trials for other conditions including polycythemia vera, juvenile idiopathic arthritis, multiple myeloma, and myelofibrosis. At this time, there is insufficient evidence of benefit in these conditions.

**Clinical Safety:**
Studies of givinostat included 222 people with DMD who were 6 years of age or older. Of these, 187 people were prescribed givinostat for over 12 months and 105 were prescribed givinostat for over 24 months.[4] In the phase 3 clinical trial, serious adverse events occurred in 7% (n=8) of people treated with givinostat, and 4 people (3%) discontinued treatment because of adverse events. Dose modifications due to adverse events occurred in 42% (n=50) of people treated with givinostat compared to 8% (n=5) of people treated with placebo.[2] Common adverse events occurring in clinical trials include gastrointestinal disturbances (e.g., diarrhea, nausea, vomiting, abdominal pain), thrombocytopenia, increased triglycerides, pyrexia and rash.[4] Myalgia, arthralgia and fatigue were also more common with givinostat compared to placebo (**Table 2**).[4] The FDA labeling includes precautions for QTc prolongation and other hematologic changes related to myelosuppression (decreased hemoglobin and neutropenia).[4] Decreased hemoglobin and neutrophil counts were observed in clinical trials, but were not associated with adverse events.[2] Risk for QTc prolongation may be increased in the setting of or underlying electrolyte disturbances, heart disease, or use of concomitant medications that increase risk for QTc prolongation. Adequate rehydration is recommended in the setting of vomiting and diarrhea to avoid electrolyte imbalances, and givinostat was not studied in people with risk factors for torsades de pointes (e.g., hypokalemia, heart failure, or family history of long QT syndrome).[4] There is no information on safety of givinostat during pregnancy as DMD predominately occurs in males. However, animal studies indicate givinostat may increase risk for fetal abnormalities and have adverse effects on reproduction.[4] Other HDAC inhibitors have been FDA-approved for T-cell lymphoma and multiple myeloma and are associated with similar cardiac arrhythmias, hematologic toxicities, and gastrointestinal adverse events.[2]

**Table 2. Common adverse events occurring with >4% of people treated with givinostat and more common than placebo.[2,4]**

| | Givinostat (n=118) | Placebo (n=61) |
|---|---|---|

| | | |
|---|---|---|
| Gastrointestinal | | |
| - Diarrhea* | 37% | 20% |
| - Abdominal pain | 34% | 25% |
| - Nausea/vomiting* | 32% | 18% |
| - Constipation | 7% | 2% |
| - Decreased appetite* | 7% | 0% |
| Blood disorders | | |
| - Thrombocytopenia* | 33% | 0% |
| - Hematoma* | 4% | 0% |
| Hypertriglyceridemia* | 23% | 7% |
| Dermatologic | | |
| - Rash* | 9% | 2% |
| - Erythema* | 4% | 0% |
| Other/general | | |
| - Pyrexia | 13% | 8% |
| - Myalgia | 9% | 3% |
| - Arthralgia* | 8% | 2% |
| - Fatigue* | 8% | 0% |
| - Dizziness* | 4% | 0% |

*FDA analysis indicated a statistically significant difference in adverse events for givinostat compared to placebo.[2]

Post-marketing requirements include the following studies: animal studies to evaluate potential carcinogenicity, a 5-year prospective observational registry study to evaluate risk for thrombocytopenia and serious bleeding events in people treated with givinostat, and pharmacokinetic studies to evaluate impact of hepatic impairment on givinostat exposure.[2] Safety in people with more advanced or severe symptoms of DMD is unknown. Heart failure is more common in people with severe symptoms of DMD, and these people were excluded from clinical trials. Gastrointestinal, triglyceride, and hematologic adverse events were generally dose related. However, amendments to the starting dose during the phase 3 clinical trial and frequent dose reductions make it difficult to assess safety of each dose. More patients treated with givinostat than placebo had elevations in creatinine (46% with givinostat vs. 12% with placebo; MD 26.5%, 95% CI 16.0 to 37.0%) and decreases of greater than 25% in estimated glomerular filtration rate (eGFR; 6% vs. 2%).[2] However, elevations in creatinine are common in DMD, and it is unclear whether these changes were related to givinostat or the underlying disease process. Serum cystatin C levels may be a more accurate indicator of renal function in people with DMD. However, people who had serum cystatin C levels more than 2 times the upper limit of normal were excluded from the clinical trial, and changes in serum cystatin C levels were not reported.

Look-alike / Sound-alike Error Risk Potential: Givinostat may be confused with givosiran, a medication indicated for acute hepatic porphyria.

**Comparative Endpoints:**

Clinically Meaningful Endpoints:
1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
2) Disease progression

Primary Study Endpoint:
1) 4-stair climb (motor function)

3) Quality of life
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

**Table 3. Pharmacology and Pharmacokinetic Properties.[2,4]**

| **Parameter** | |
|---|---|
| Mechanism of Action | Givinostat is a histone deacetylase inhibitor. Histone deacetylase affects protein expression through unraveling DNA, binding to transcription factors and affecting synthesis of mRNA.[2] Givinostat upregulates follistatin resulting in increased muscle generation.[2] In DMD, this reduces the fraction of healthy muscle cells that are replaced with fatty or fibrous tissue.[3] |
| Oral Bioavailability | Bioavailability was not reported, time to maximum plasm concentrations was 2-3 hours; high fat meal increased exposure 40% increase in AUC and 23% increase in maximum concentration. |
| Distribution and Protein Binding | Protein binding: 96% |
| Elimination | Extensively metabolized in the liver. Less than 3% is excreted unchanged in the urine. 61% of inactive metabolites excreted in the urine. |
| Half-Life | 6 hours |
| Metabolism | Extensively metabolized into inactive metabolites. Metabolism did not involve CYP450 enzymes. |

Abbreviations: AUC = area under the curve; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; mRNA = messenger ribonucleic acid

**Table 4. Comparative Evidence Table.**

| **Ref./ Study Design** | **Drug Regimens/ Duration** | **Patient Population** | **N** | **Efficacy Endpoints** | **ARR/ NNT** | **Safety Outcomes** | **ARR/ NNH** | **Risk of Bias/ Applicability** |
|---|---|---|---|---|---|---|---|---|
| 1. Mercuri, et al. 2024.[3]<br><br>FDA review[2]<br><br>MC, DB, PC, phase 3, RCT<br><br>EPIDYS trial NCT02851797 | 1. Gininostat twice daily<br><br>2. Placebo<br><br>Flexible, weight-based dosing. Dose reductions were permitted for adverse events. (starting dose was initially 20-70 mg BID. After an interim safety analysis, dose | Demographics:<br>- Age: 9.8 years<br>- White: 91%<br>- Time since diagnosis: 5 years<br>- BMI: 19-20 kg/m$^2$<br>- DMD mutation<br>Deletion: 67%<br>Duplication: 17%<br>Point mutation: 14%<br>- Corticosteroid<br>Deflazacort daily: 69%<br>Other daily steroid: 13%<br>- 4-stair climb: 3.4 s<br><br>Key Inclusion Criteria: | ITT:<br>Total<br>1. 118<br>2. 61<br><br>Group A:<br>1. 81<br>2. 39<br><br>Group B:<br>1. 37<br>2. 22<br><br>Attrition:<br>1. 7(6%)<br>2. 2(3%) | Primary Endpoint (change after 72 weeks in group A):<br>Mean change in time to climb 4-stairs (s)<br>1. 1.25 (95% CI 0.31 to 2.18)<br>2. 3.03 (95% CI 1.67 to 4.39)<br>LSMD -1.78 (95% CI -3.46 to -0.11); p=0.037<br><br>Re-analysis using MMRM for missing data: LSMD -1.64 s, SE 0.94, p=0.083, NS<br><br>Secondary Endpoints (change after 72 weeks in group A):<br>Change in mean NSAA score<br>1. -2.66 (95% CI -3.56 to -1.76)<br>2. -4.58 (95% CI -5.89 to -3.26) | NA | Serious AE<br>1. 8 (7%)<br>2. 2 (3%)<br><br>DC due to AE<br>1. 4 (3%)<br>2. 0 (0%)<br>MD 3.4% (95% CI 0.1 to 6.7)<br><br>Dose modification due to AE[2]<br>1. 50 (42%)<br>2. 5 (8%)<br>MD 34.2% (95% CI 22.9 to 45.4) | NS<br><br>3%/30<br><br>34%/3 | **Risk of Bias (low/high/unclear)**:<br>Selection Bias: Unclear. Randomized via interactive response technology and stratified based on corticosteroid use. Patients randomized to givinostat were more likely to be prescribed a daily corticosteroid (84% vs. 78%), less likely to have duplication mutations (14% vs. 23%) and more likely to have a point mutation (15% vs. 11%).<br>Performance Bias: High. Blinded with use of matched placebo (appearance and taste). Dose reductions due to adverse events may have led to unblinding. Performance on motor function tests is highly dependent on motivating factors and method of administration.<br>Detection Bias: High. Participants, providers, site staff were masked to treatment. Different staff conducted efficacy analyses and recorded safety results to mitigate unmasking related to adverse effects (e.g., low platelet counts). Success of masking was not assessed. Functional tests were evaluated by trained physiotherapists. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | was reduced to 13.3-46.7 mg BID).<br><br>Duration: 72 weeks<br><br>Group A: baseline VLFF between 5% and 30% to identify people who were not at risk of sudden loss of ambulation but who were at risk of motor function decline<br><br>Group B: baseline VLFF ≤5% or >30%<br><br>Randomization 2:1 | - Males with genetically confirmed DMD<br>- Age ≥ 6 years<br>- Ambulatory<br>- 4-stair climb ≤ 8 s (mean of 2 tests with ≤1 s variance)<br>- Time to rise 3-10 s<br>- Prescribed corticosteroids ≥ 6 months<br>- Manual muscle testing of quadriceps grade ≥ 3<br><br><u>Key Exclusion Criteria</u>:<br>- Surgery, changes in medication, or contracture therapy (serial casting, night splints, stretching exercises) within 3 months that may impact muscle function or strength<br>- Loss of ankle plantar flection ≥30$^{o}$<br>- Other targeted therapy for DMD<br>- Low platelets, WBC or hemoglobin levels, triglycerides >300 mg/dL<br>- QTc >450 milliseconds<br>- Liver disease, inadequate renal function (serum cystatin C >2x ULN)<br>- Heart failure NYHA class II-IV or LVEF <50% | | LSMD 1.91 (95% CI 0.30 to 3.53)*<br><br>Cumulative loss of function for items on the NSAA scale (17 items at each visit; 102 items total)<br>1. 3.42 (95% CI 2.69 to 4.33)<br>2. 5.56 (95% CI 4.00 to 7.72)<br>LSMD 2.14; ratio 0.61 (95% CI 0.41 to 0.93)*<br><br>Time to rise (s)<br>1. 9.33 (95% CI 5.82 to 12.84)<br>2. 12.61 (95% CI 7.49 to 17.72)<br>LSMD –3.28 (95% CI -9.57 to 3.02)<br><br>6MWT (m)<br>1. -38.4 (95% CI -50.7 to -26.2)<br>2. -48.4 (95% CI -66.3 to -30.5)<br>LSMD 10.0 (95% CI -12.1 to 32.0)<br><br>Knee extension (N/kg)<br>1. -0.32 (95% CI -0.44 to -0.20)<br>2. -0·50 (95% CI -0.68 to -0.33)<br>LSMD 0.19 (-0.03 to 0.40)<br><br>Elbow flexion (N/kg)<br>1. -0.10 (95% CI -0.17 to -0.03)<br>2. -0.19 (95% CI -0.29 to -0.09)<br>LSMD 0.09 (-0.04 to 0.21)<br><br>* NSAA scores favored givinostat but were not statistically significant after multiplicity adjustment based on the pre-specified statistical analysis plan. The study was not powered to determine differences in secondary endpoints. | | Low platelets/ thrombocytopenia (<lower limit of normal)<br>1. 39 (33%)<br>2. 0 (0%)<br>MD 33.1% (95% CI 24.6 to 41.5)<br><br>Mean change in platelets[2] (x $10^{9}$ cells/L)<br>1. -100.6 (SD 61.7)<br>2. -1.2 (SD 62.8)<br><br>High triglycerides/ hypertriglyceridemia (< lower limit of normal)<br>1. 27 (23%)<br>2. 4 (7%)<br>MD 16.3% (95% CI 6.5 to 26.1)<br><br>Mean change in triglyceride levels (mmol/L)[2]<br>1. 0.5 (SD 0.774)<br>2. 0.18 (SD 0.687) | 33%/4<br><br>NA<br><br>16%/7<br><br>NA | <u>Attrition Bias</u>: High. Overall attrition was low. Primary outcome data was missing for 13 patients at 18 months (11%). Missing values were imputed based on a single-value average from other participants in the group for that timepoint. This method ignores the potential uncertainty of imputed values and may create an artificially narrow measure of variance.[2] When reanalyzed based on a mixed method repeated measures model including all observed data, results showed similar magnitude of effect, but wider variance, and were no longer statistically significant (MD -1.64 s, SE 0.94, p=0.083).[2] Secondary outcome analyses for NSAA were less sensitive to missing data.<br><u>Reporting Bias</u>: Low. Statistical analysis plan amended before unmasking to include baseline covariates for efficacy analyses and analyze velocity for timepoint endpoints. Pre-specified testing plan to control for multiplicity and type 1 error for secondary endpoints. The study was not powered to determine differences in secondary endpoints.<br><u>Other Bias</u>: Unclear. Study sponsor was involved in study design, data analysis, collection, interpretation, and manuscript preparation.<br><br>**Applicability**:<br><u>Patient</u>: Of 359 people screened, 179 were enrolled (50%). The most common reasons for screening failure were predicted VLFF outside of the specified range (10-30%), rise from floor time <3 seconds, and >30$^{o}$ loss of plantar flexion.[2] The primary analysis (Group A) was conducted in people who were at risk of motor function decline, but who were not at risk of sudden loss of ambulation based on their vastus lateralis fat fraction. Most participants identified as White; other racial groups were underrepresented. Analysis of data in Group B demonstrated a similar direction of effect, although the population was small and underpowered to detect differences between groups.<br><u>Intervention</u>: The studied dose was weight-based and ranged from 20-70 mg twice daily. Dose was reduced to 13.3-47.7 mg following an interim safety analysis that identified 50-60% of patients had reduced dose due to low platelets. The FDA-approved initial dose is weight-based (range 22.2-53.2 mg BID) and was developed as a simplified dosing regimen. FDA analysis of cumulative exposure indicated a dose-relationship with higher exposure and improvement on 4 stair climb and NSAA. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Comparator: Placebo appropriate to determine efficacy. All patients were prescribed concomitant corticosteroids, the current standard of care for DMD.<br>Outcomes: Outcomes were appropriate to evaluate motor function and were evaluated every 12 weeks.<br>Setting: Participants were from 41 sites in 11 countries enrolled between June 2017 and February 2022. About 24% of patients were from the United States. |

Abbreviations: 6MWT = 6-minute walk test; AE = adverse event; ARR = absolute risk reduction; BID = twice daily; BMI = body mass index; CI = confidence interval; DB = double blind; DC = discontinue; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; ITT = intention to treat; LSMD = least squares mean difference; LVEF = left ventricular ejection fraction; MC = multicenter; MD = mean difference; MMRM = mixed model for repeated measures; N = number of subjects; N/kg = Newtons per kilogram; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; NSAA = North Star Ambulatory Assessment; NYHA = New York Heart Association; PC = placebo-controlled; PP = per protocol; QTc = QT interval; RCT = randomized controlled trial; s = second; SD = standard deviation; SE = standard error; ULN = upper limit of normal; VLFF = vastus lateralis fat fraction; WBC = white blood cell

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38. Vyondys 53 (golodirsen injection) [package insert] Cambridge, MA: Sarepta Therapeutics, Inc.; June 2024.

**Appendix 1:** Current Preferred Drug List

| Brand | Generic | Form | Route | PDL |
|---|---|---|---|---|
| AMONDYS-45 | casimersen | VIAL | Intravenous | N |
| DEFLAZACORT | deflazacort | ORAL SUSP | Oral | N |
| EMFLAZA | deflazacort | ORAL SUSP | Oral | N |
| DEFLAZACORT | deflazacort | TABLET | Oral | N |
| EMFLAZA | deflazacort | TABLET | Oral | N |
| ELEVIDYS | delandistrogene moxeparvc-rokl | KIT | Intravenous | N |
| ELEVIDYS | delandistrogene moxeparvc-rokl | VIAL | Intravenous | N |
| EXONDYS-51 | eteplirsen | VIAL | Intravenous | N |
| DUVYZAT | givinostat hydrochloride | ORAL SUSP | Oral | N |
| VYONDYS-53 | golodirsen | VIAL | Intravenous | N |
| AGAMREE | vamorolone | ORAL SUSP | Oral | N |
| VILTEPSO | viltolarsen | VIAL | Intravenous | N |

**Appendix 2:** Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to July 25, 2024

| | | |
|---|---|---|
| 1 | eteplirsen.mp. | 180 |
| 2 | golodirsen.mp. | 53 |
| 3 | exp Glucocorticoids/ | 210888 |
| 4 | deflazacort.mp. | 654 |
| 5 | Muscular Dystrophy, Duchenne/ | 7556 |
| 6 | viltolarsen.mp. | 49 |
| 7 | vamorolone.mp. | 38 |
| 8 | casimersen.mp. | 27 |
| 9 | delandistrogene moxeparvovec.mp. | 12 |
| 10 | givinostat.mp. | 148 |
| 11 | 1 or 2 or 3 or 4 or 6 or 7 or 8 or 9 or 10 | 211617 |
| 12 | 5 and 11 | 540 |
| 13 | limit 12 to (english language and humans) | 464 |
| 14 | limit 13 to yr="2023 -Current" | 54 |

**Appendix 3:** Prescribing Information Highlights

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use DUVYZAT safely and effectively. See full prescribing information for DUVYZAT.**

**DUVYZAT (givinostat) oral suspension**
**Initial U.S. Approval: 2024**

**----------INDICATIONS AND USAGE----------**
DUVYZAT is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older. (1)

**----------DOSAGE AND ADMINISTRATION----------**
- Obtain and evaluate baseline platelet counts and triglycerides prior to initiation of DUVYZAT. Do not initiate DUVYZAT in patients with a platelet count less than 150 x 10^9/L. (2.1, 5.1, 5.2)
- The dosage of DUVYZAT is based on patient's body weight. (2.2)
- Administer orally twice daily with food. (2.2)
- Dosage modifications may be needed for decreased platelet counts, diarrhea, increased triglycerides, or QTc prolongation. (2.3, 5.1, 5.2, 5.3, 5.4)

**----------DOSAGE FORMS AND STRENGTHS----------**
Oral suspension: 8.86 mg/mL givinostat. (3)

**----------CONTRAINDICATIONS----------**
None. (4)

**----------WARNINGS AND PRECAUTIONS----------**
- Hematological Changes: DUVYZAT can cause dose-related thrombocytopenia and other signs of myelosuppression, including anemia and neutropenia. Monitor platelets; dosage adjustment or discontinuation may be needed. (2.3, 5.1)
- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed. (2.3, 5.2)
- Gastrointestinal Disturbances: Adjust dosage if moderate or severe diarrhea occurs. Antiemetics or antidiarrheal medications may be considered during treatment with DUVYZAT. Discontinue DUVYZAT if the symptoms persist. (2.3, 5.3)
- QTc Prolongation: Avoid use of DUVYZAT in patients who are at an increased risk for ventricular arrhythmias. (2.1, 5.4, 7.2)

**----------ADVERSE REACTIONS----------**
Most common adverse reactions (≥10% in DUVYZAT-treated patients) are diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact ITF Therapeutics, LLC. at 1-800-664-1490 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**
- Closely monitor when DUVYZAT is used in combination with an oral CYP3A4 sensitive substrate or a sensitive substrate of the OCT2 transporter, for which a small change in substrate plasma concentration may lead to serious toxicities. (7.1)
- Avoid concomitant use with other drugs that prolong the QTc interval; monitor ECG if concomitant use cannot be avoided. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Hepatic Impairment: Exposure to givinostat is expected to be increased. (8.6)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 3/2024**

**Appendix 4:** 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; motor, cardiac or lung function; quality of life; disability or hospitalization; disease progression; mortality |
| **Setting** | Outpatient |

**Appendix 5:** Prior Authorization Criteria

# 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<br><br>Results of genetic testing are required for approval. | **No:** Pass to RPh. Deny; medical appropriateness.<br><br>Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses. |

| Approval Criteria | | |
|---|---|---|
| 3. Is the medication prescribed by a neuromuscular specialist? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 4. Is the request for an FDA approved age (i.e., 4 years or older)? | **Yes:** Go to #5 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 5. Does the patient have deletions of exon 8 or 9? | **Yes:** Pass to RPh. Deny; medical appropriateness. | **No:** Go to #6 |
| 6. 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?<br><br>Note: these populations were excluded from clinical studies and may have increased risk for severe immune-mediated myositis reactions. | **Yes:** Go to #7 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 7. Has baseline testing been completed and is within normal limits?<br><br>Recommended baseline testing includes testing for anti-AAVrh74 antibodies (by ELISA), troponin-I, platelets, and liver function tests. | **Yes:** Go to #8<br><br>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. | **No:** Pass to RPh. Deny; medical appropriateness. |
| 8. Has the patient received, or have contraindications to, all routine immunizations recommended for their age?<br><br>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. | **Yes:** Go to #9<br><br>Document provider attestation of immunization history. | **No:** Pass to RPh. Deny; medical appropriateness. |

| Approval Criteria | | |
|---|---|---|
| 9. Is the patient able to tolerate an elevated dose of prednisone for at least 60 days and complete necessary ongoing monitoring? | **Yes:** Go to #10<br><br>Document provider attestation. | **No:** Pass to RPh. Deny; medical appropriateness. |
| 10. Is there documentation that the provider and member have discussed potential risks of treatment?<br><br>Note: Informed consent is recommended as this therapy has shown that it does not change global motor function in 2 clinical trials. It is associated with serious side effects including injury to the liver and heart and it may prevent use of any future adeno-based gene therapy. | **Yes**: Go to #11 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 11. Has the patient received a prior dose of an adeno-based gene therapy? | **Yes:** Pass to RPh. Deny; medical appropriateness. | **No:** Approve single infusion (max 1 dose per lifetime) |

*P&T/DUR Review:* *10/24, 2/24 (SS)*
*Implementation:* *12/1/2024; 4/1/24*

# 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 (DMD).
- 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 or histone deacetylase (HDAC) inhibitors (see Table 1; pharmacy or physician administered claims)
- Non-preferred corticosteroids that are FDA-approved for Duchenne muscular dystrophy (e.g., deflazacort, vamorolone, 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) | Recommended safety monitoring |
|---|---|---|---|
| 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 | Renal function (e.g., serum cystatin C, urine dipstick, and urine protein-to-creatinine) within the past 3 months |
| 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 | None |
| 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 | Renal function (e.g., serum cystatin C, urine dipstick, and urine protein-to-creatinine) within the past 3 months |
| 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 | |
| givinostat (Duvyzat®) | Genetically confirmed Duchenne muscular dystrophy | No specific restrictions for type of mutation | Fasting triglycerides <300 mg/dL, platelet count > 150 x$10^9$ cells/L for all patients, and ECG in people with heart disease or cardiac risk factors within the past 3 months |

Table 2. Minimum recommended givinostat doses

| Weight | Minimum recommended dose |
|---|---|
| 10 to <20 kg | 13.3 mg twice daily |
| 20 to <40 kg | 17.7 mg twice daily |
| 40 to <60 kg | 26.6 mg twice daily |

| | |
|---|---|
| ≥ 60 kg | 35.4 mg twice daily |

| **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.<br><br>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?<br><br>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<br><br>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?<br><br>Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use. | **Yes:** Approve for up to 12 months.<br><br>Document contraindication or intolerance reaction. | **No:** Pass to RPh. Deny; medical appropriateness.<br><br>Recommend trial of prednisone. |

| Approval Criteria | | |
|---|---|---|
| 7. Is the request for givostat? | **Yes:** Go to #8 | **No:** Go to #9 |
| 8. Is the requested dose at or above the minimum recommended FDA dose (Table 2)?<br><br>Note: Discontinuation of givostat is recommended if adverse events persist despite dose reduction. There is no evidence evaluating efficacy of lower doses. | **Yes**: Go to #9 | **No:** Pass to RPh, Deny; medical appropriateness. |
| 9. Is the request for continuation of treatment previously approved by FFS? | **Yes:** Go to **Renewal Criteria** | **No:** Go to #10 |
| 10. Is the request for an FDA-approved indication (Table 1)? | **Yes:** Go to #11<br><br>Document genetic testing. | **No:** Pass to RPh, Deny; medical appropriateness. |
| 11. Is the request for combination treatment with 2 or more targeted therapies?<br><br>There is no data evaluating combined use of targeted treatments for Duchenne Muscular Dystrophy. | **Yes:** Pass to RPh. Deny; medical appropriateness. | **No:** Go to #12 |
| 12. Has baseline testing been completed as recommended in the FDA label (Table 1)? | **Yes**: Go to #13 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 13. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids? | **Yes:** Go to #14 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 14. 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. Has the provider performed safety monitoring as recommended in the FDA label (Table 1)?<br><br>Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatine ratio every 3 months. | **Yes:** Go to #2 | **No:** Pass to RPh, Deny; medical appropriateness. |
| 2. 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? | **Yes:** Go to #3<br><br>Document functional status and provider attestation. | **No:** Pass to RPh, Deny; medical appropriateness. |
| 3. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, low platelets, high triglycerides, etc.)? | **Yes:** Go to #4 | **No:** Approve for up to 6 months |
| 4. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)? | **Yes:** Approve for up to 6 months<br><br>Document provider attestation | **No:** Pass to RPh, Deny; medical appropriateness. |

*P&T/DUR Review:* *10/24, 2/24; 8/21 (SS); 2/21; 6/20; 09/19; 11/17; 07/17*
*Implementation:* *12/1/2024; 4/1/24; 9/1/21; 3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17*