Anthem

Medical Policy

Subject: Gene Therapy for Duchenne Muscular Dystrophy
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Description/Scope

This document addresses gene therapy for Duchenne muscular dystrophy (DMD), a rare and serious genetic disease affecting muscle strength and movement. Gene therapy is being proposed as a one-time treatment to significantly lessen the severity of DMD. At this time, one gene therapy has been approved by the Food and Drug Administration (FDA) to treat DMD: delandistrogene moxeparvovec-rokl (ELEVIDYS), an adeno-associated virus vector-based gene therapy.

Note: Please refer to the applicable clinical pharmacy criteria used by the Plan for information regarding disease-modifying treatments for DMD; for example: casimersen (Amondys 45), viltolarsen (Viltepso), and golodirsen (Vyondys 53).

Position Statement

Medically Necessary:

A one-time infusion of delandistrogene moxeparvovec-rokl (ELEVIDYS) is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene; **and**
B. No deletion in exon 8 or exon 9 in DMD gene; **and**
C. Ambulatory; **and**
D. Age 4 through 5 years (at least 4 years 0 days and less than 6 years old); **and**
E. Anti-AAVrh74 total binding antibody titers less than 1:400; **and**
F. Absence of active infection; **and**
G. Absence of significant liver dysfunction or disease, defined as *at least one of the following*:
    1. Preexisting liver impairment; **or**
    2. Chronic hepatic condition; **or**
    3. Acute liver disease (e.g., acute hepatic viral infection).

Investigational and Not Medically Necessary:

Delandistrogene moxeparvovec-rokl (ELEVIDYS) is considered **investigational and not medically necessary** when the criteria above are not met.

Rationale

Duchenne Muscular Dystrophy (DMD)

Muscular dystrophy (MD) refers to a diverse group of genetic conditions characterized by a decrease in muscle mass over time, including progressive damage and weakness of facial, skeletal, breathing, and heart muscles. Duchenne muscular dystrophy (DMD), the most common and one of the most severe forms of inherited muscular dystrophies, is caused by a mutation of the DMD gene. The DMD gene is responsible for regulating the production of the dystrophin protein that helps keep muscles cells intact. In DMD, the lack of dystrophin weakens the link between the cytoskeleton and sarcolemma which then causes damage to the muscle fibers during contraction and leads to a cycle of muscle cell degeneration, inflammation, fibrosis, and inhibition of muscle fiber regeneration. This process results in progressive deterioration of muscle quality, mass and resulting weakness of facial, limb, respiratory, and cardiac muscles (Darras, 2022; Deng, 2022).

DMD is a rare, X-linked condition, occurring in approximatley1 in 5000 males born worldwide. The DMD gene is located on the X chromosome, and most cases are caused by carriers (mothers) passing the mutation to sons. The remaining one-third of DMD cases are the result of spontaneous mutations that take place on the X chromosome. If a female inherits a dystrophin

mutation on one of her X chromosomes, she typically gets sufficient dystrophin from her functioning gene on the other X chromosome but will be a carrier for the disease (Mendell, 2012; Moat, 2013).

While disease progression is variable, muscle weakness is usually noticeable in early childhood. Early signs may include delayed ability to sit, stand, or walk and problems learning to speak. Individuals may be wheelchair-dependent by adolescence. The loss of strength in active breathing muscles leads to respiratory insufficiency and the need for ventilation in the teenage years. Affected individuals infrequently survive beyond the third decade, with respiratory complications and progressive cardiomyopathy being the most common causes of death (Bello, 2026; Landfeldt, 2020; McDonald, 2018; Szabo,2022).

Several objective measures of motor function have been used to monitor clinical progression for individuals with DMD and to assess the effects of proposed treatments. The North Star Ambulatory Assessment (NSAA) is one such measure that consists of 17 activities including standing, walking, running, and rising from the floor or from a chair, as well as other activities. Each activity is scored as 2 – no limitation, 1 – modified activity but able to independently complete, or 0 – unable to complete the activity independently. The highest achievable score for the 17 activities is 34. The NSAA has been validated in a variety of settings.

The FDA Briefing document for their 2023 PMA approval for delandistrogene moxeparvovec-rokl states that, in general, individuals with DMD show improvements on the NSAA until about age 6, and then begin to decline. NSAA results can be affected both by the consistency of administration (process-dependent) and by the effort of the participant and/or encouragement or coaching received from a family member, caregiver, or medical team (effort-dependent). Therefore, blinding to treatment assignment is preferred in clinical studies employing the NSAA to limit detection bias.

Gupta and colleagues used several methods to estimate the minimal clinically important difference (MCID) for the NSAA measured in individuals with DMD who were aged 7 – 13 years (Gupta, 2023). Their methods included statistical analysis as well as validating interviews with participants and their parents. Their estimate of the MCID for NSAA for participants aged 7 to 10 years was a score difference of 2.3 – 2.9 points when based on distribution-based estimates of 1/3 standard deviation. The estimated MCID was between 2.9 and 3.5 points when based on the standard error of measurement. When anchored on the 6-minute walk distance (6MWD), the MCID was 3.5 points. The questionnaires showed that the participants rated as significant any loss of function (reduction to a zero score for an activity) or reduction in function (change from a score of 2 to a score of 1) in 1 or 2 activities.

A report published by Ricotti and colleagues in 2016 evaluated the NSAA rate of decline in DMD stratified for different DMD genetic mutations and for the timing of the initiation of glucocorticoid therapy. These investigators used a linearized version of the NSAA. The linearized version converts the NSAA score from a range of 0 – 34 to a range of 0 -100. The authors propose that this conversion improves the comparability of changes across the range. They state that “whereas with the raw score a drop of several points at a mid-level of ability might actually mean a small loss of function (difficulty getting on and off a small step but still independently) and a drop of one point at either end of the scale might suddenly mean a loss of independence rising from the floor or loss of ability to run.” Ricotti, et al., cited a 2013 paper by Mayhew and colleagues to state that the MCID for the linearized NSAA is approximately 10 units. The Ricotti study found an average annual decline in linearized NSAA scores of about 8 units per year after the age of 7. This correlates with a loss of about 4 raw score points per year. Individuals who started glucocorticoid therapy between 3 and 5 years of age experienced an average increase in linearized NSAA score of 3 units/year (1.3 raw unit score increase/year) up until around age 7.

In 2019, Muntoni and colleagues (2019) published results of 395 individuals with DMD in the United Kingdom to establish the natural progression of the NSAA score over time. Participants in the database fell into 1 of 4 clusters: Cluster 1 (25% of all participants) experienced rapid progression with NSAA score falling to <5 by age 10; Cluster 2 included 35% of the total and showed a reduction of their NSAA score to <5 by age 12; Cluster 3 (21%) experience a fall in the NSAA score to <5 by age 14; and Cluster 4 (19%) maintained an NSAA score above 5 past their 15^{th} birthdays. The authors estimated that approximately 40% of children diagnosed with DMD will continue in a “maturation phase” after the age of 7, during which time their NSAA scores would continue to rise.

In 2016, Mercuri and colleagues published a study evaluating the natural history of performance on the 6MWD test by individuals with DMD. They noted previous studies showing that “rates of change in 6MWD showed significantly greater cross-patient variability than expected, resulting in limited statistical power to measure treatment effects with available sample sizes.” The group studied 96 children aged 5 to 17 years with a mean age of 8.3 years. Almost 65% of the participants had a 6MWD of 350 meters or more at the start of the study. Almost all (96%) were receiving systemic steroids. Similar to the work by Muntoni on the trajectory of NSAA scores, Mecuri found that the observed high variability of the 3-year change in 6MWD could be reduced by grouping participants into trajectory classes. They propose that “an accurate prediction model for trajectories of ambulatory function would enable improved enrichment, stratification, baseline adjustment, and matching in clinical trials with randomized or natural history controls.”

Currently there is no cure for DMD, but improvements in treatment care and management are able to slow disease progression and improve quality of life, thereby prolonging life expectancy for affected individuals (Darras, 2022; Deng, 2022).

Gene Therapy for Duchenne Muscular Dystrophy (DMD)

Delandistrogene moxeparvovec-rokl (ELEVIDYS [Sarepta Therapeutics, Inc. Cambridge, MA]) is a gene therapy for individuals with DMD, initially approved by the FDA under an accelerated approval program on June 22, 2023, for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene. ELEVIDYS is administered as a one-time gene transfer infusion using the adeno-associated virus serotype rh74 (rAAVrh74) vector to deliver the micro-dystrophin-encoding gene to skeletal and cardiac muscle tissue. Cells that receive the modified gene produce a micro-dystrophin (a shortened form of the naturally occurring dystrophin protein). Researchers believe that recipients of the modified dystrophin gene will have a milder, Becker-type muscular dystrophy phenotype.

Throughout the FDA approval process, delandistrogene moxeparvovec-rokl has been variably referred to using that name, it's product development code SRP-9001, rAAVrh74.MHCK7 micro-dystrophin, or its brand name ELEVIDYS. Although there may be differences related to the evolving pharmaceutical production process, this document considers that all 4 names refer to the same product that we will refer to as ELEVIDYS.

Clinical Trial SRP-9001-101 (NCT03375164)

At the time of this review, there is only one published study evaluating the safety and biologic efficacy of the administration of ELEVIDYS in boys with DMD (NCT 03375164) . In this open-label, phase I/IIa, non-randomized, controlled trial, Mendell and colleagues (2020) reported on the safety and tolerability of intravenous ELEVIDYS (referred to as rAAVrh74.MHCK7.micro-dystrophin) in individuals with DMD at 52 weeks following treatment. Researchers assessed the number of participants with adverse events following the IV administration of ELEVIDYS for the treatment of DMD. Secondary outcome measures included: 100-meter timed test; change from baseline of micro-dystrophin gene expression quantification as measured by immunofluorescence; and baseline of micro-dystrophin gene expression quantification as quantified by Western blot test.

This study enrolled 4 ambulatory individuals between the ages of 4 to 7 years of age with DMD showing a frameshift mutation contained between exons 18 and 58 (inclusive). These participants were required to have had no preexisting AAVrh74 antibodies, to have received a stable corticosteroid dose for 12 or more weeks, and to be able to cooperate with motor assessment testing . All participants were sufficiently ambulatory to complete several motor assessments. Muscle function was evaluated using the NSAA, a 17-item measure of ambulatory functions with a score range of 0 (unable) to 34 (perfect score). Other functional outcomes evaluated included time to rise from floor, time to ascend four steps, 100-meter timed test, and handheld dynamometry for knee extensors and flexors as well as elbow extensors and flexors (Mendell, 2020).

On day 1 of the trial, all participants received 2.0×10^{14} vg/kg ELEVIDYS infusion. A total of 53 adverse events were reported of which 33 (62%) were considered mild and 20 (38%) were considered moderate. While no serious adverse events were reported, 18 adverse events were deemed treatment related, the most common of which was vomiting (9 of 18 events [50%]). A total of 3 participants had transiently elevated γ-glutamyltransferase, which resolved with corticosteroids. At 12 weeks, immunohistochemistry of gastrocnemius muscle biopsy specimens demonstrated transgene expression in all participants, with a mean of 81.2% of muscle fibers expressing micro-dystrophin. Western blot revealed a mean expression of 74.3% without fat or fibrosis adjustment and 95.8% with adjustment. At enrollment, the participants' mean (standard deviation [SD]) NSAA score was 20.5 (3.7) points. The 1-year NSAA score improved 7, 8, 2 and 5 points (mean, 5.5 points) in participants 1, 2, 3 and 4, respectively. All participants had confirmed vector transduction and reduced creatine kinase levels (posttreatment vs baseline) that were maintained for 1 year. The authors concluded that the study demonstrated ELEVIDYS could be delivered safely and resulted in no major adverse events. Expression of micro-dystrophin protein and decreased creatine kinase levels were also demonstrated (Mendel, 2020).

Although the results of NCT 03375164 demonstrated that the 1-year NSAA score improved by a mean of 5.5 points, it is important to note that a clinically meaningful difference in NSAA scores (approximately 10-point change) was not reached (Ricotti, 2016). In this study, ELEVIDYS treatment began at age 4, during the period of time when individuals with DMD would be expected to be improving. As previously noted, blinding to treatment assignment is preferred in clinical studies employing the NSAA. Larger, controlled and blinded studies with longer follow-up are needed to demonstrate clinically meaningful improvement in functionality (U.S. FDA 2023a).

Clinical Trial SRP-9001-102 (NCT03769116)

As part of the unpublished data submitted to the FDA in support of the BLA in SRP-9001-102 (Study 102), researchers reported results of statistical analysis of an ongoing, randomized, double-blind, placebo- controlled, multicenter, 3-part clinical study in 41 ambulatory individuals with DMD with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the DMD gene. All participants were 4 years or older and less than 8 years of age at time of

infusion in Part 1. The primary objectives of this 3-part study were to evaluate micro-dystrophin expression at 12 weeks following ELEVIDYS infusion as measured by western blot of biopsied muscle tissue expressed as a percent of control (levels of dystrophin in normal participants without DMD or Becker muscular dystrophy [BMD]) and to evaluate the effect of ELEVIDYS on physical function as assessed by the NSAA over 48 weeks. In Part 1, participants were randomized 1:1 to receive either a single intravenous infusion of SRP-9001 (n=20) or placebo (n=21). The study met its primary biological endpoint of micro-dystrophin protein expression. At Week 12 of Study 102 Part 1, the mean (SD) change from baseline levels of micro-dystrophin (% of control) were 3.6 (5.7), 28.2 (52.2), and 43.4 (48.6) for participants receiving ELEVIDYS-dose level 1 (DL1), ELEVIDYS-dose level 2 (DL2), and ELEVIDYS-dose level 3 (DL3), respectively. The study did not demonstrate a statistically significant change in NSAA from baseline to Week 48 after treatment (U.S. FDA 2023a).

Age is known to be a critical prognostic factor in the progression of DMD. Serepta Therapeutics conducted a subgroup analysis to further evaluate the treatment effect of ELEVIDYS on NSAA scores from baseline to Week 48 by stratifying participants into two age groups: 4-5 years old and 6-7 years old. The exploratory subgroup analyses demonstrated that for individuals in the age 4-5 years cohort, the least square (LS) mean changes (standard error [SE]) in NSAA total score from baseline to Week 48 were 4.3 (0.7) and 1.9 (0.7) points for the ELEVIDYS and placebo group, respectively. For participants 6-7 years of age, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) and 0.5 (0.7) points for the ELEVIDYS and placebo group, respectively. The analyses suggested that participants 4-5 years old receiving ELEVIDYS did better than the participants receiving placebo; however, individuals 6 to 7 years old who received ELEVIDYS demonstrated no improvement in NSAA and did worse than those receiving placebo. This raises the questions of whether ELEVIDYS only benefits ambulatory individuals below a certain age or above some threshold functional status. The data suggests a potential benefit of treatment with ELEVIDYS in the 4-5 years of age cohort, but potentially no benefit in individuals 6-7 years of age (U.S. FDA 2023a).

A significant limitation in Study 102 Part 1 resulted from shortcomings in dose determination, discovered following subsequent analysis that revealed three different doses of ELEVIDYS were administered to the 20 participants in the active treatment group: 6 participants received one-half the intended dose, 6 participants received two-thirds the intended dose, and 8 participants received the full intended dose.

In Part 2, which was also blinded, participants who received placebo in Part 1 received ELEVIDYS and those that had previously received ELEVIDYS received a placebo infusion. All participants were followed for another 48 weeks while safety and efficacy were evaluated. Two participants had substantially high micro-dystrophin baseline values which, according to Sarepta Therapeutic's BLA application, may have been caused by baseline expression of a nonfunctional truncated form of dystrophin resulting from participant's specific mutations. The two participant's micro-dystrophin expression results were excluded from analysis. At Week 12 of Part 2, the mean (SD) change from baseline levels of the micro-dystrophin (% of control) were 10.6 (17.0), 10.4 (14.7), and 43.5 (55.6) for participants receiving ELEVIDYS-dose level 1, ELEVIDYS-DL2 dose level 2, and ELEVIDYS dose level 3, respectively. ELEVIDYS-treated participants from the placebo crossover group (n=20, aged 5-8 at time of dosing ELEVIDYS) scored a statistically significant 2.0 points higher on the mean NSAA at 48 weeks compared to propensity-score weighted external controls (p value=0.0009). Mean NSAA scores from these Part 2 participants improved 1.3 points from baseline for the ELEVIDYS-treated group, and the NSAA scores in the external control group (n=103) declined 0.7 points from baseline. The mean age of the participants who received ELEVIDYS was 7.24 years of age.

Clinical Trial SRP-9001-103 (NCT04626674, Endeavor trial)

Study 103 (ENDEAVOR) is an open-label, Phase 1b study evaluating over a 5-year (260 weeks) period the safety of and expression from ELEVIDYS (referred to as SRP-9001 in this trial) in males at least 3 years of age with DMD. The primary outcome is the change from baseline in the quantity of micro-dystrophin protein expression at week 12 as measured by western blot (time frame from baseline to week 12). Estimated study completion date is January 2028 (U.S. FDA 2023a).

Clinical Trial SRP-9001-301 (NCT05096221, Embark trial)

The Embark trial is a global Phase 3, randomized, double blinded, placebo-controlled, Part 1 and a 52-week crossover Part 2. Participants randomized to the placebo arm in Part 1 will have an opportunity for treatment with gene transfer therapy in Part 2. The primary efficacy outcome measure in Study 301 Part 1 is the change in NSAA total score from baseline to Week 52. Study 301 is fully enrolled with 125 male participants with DMD who are 4 years or older and less than 8 years of age at time of ELEVIDYS infusion. The manufacturer proposes that Study 301 Part 1 serve as the confirmatory study should ELEVIDYS receive accelerated approval. Topline results from Study 301 Part 1 are expected in the latter part of 2023. The projected study completion date is November 2024 (U.S. FDA 2023a).

As of August 8, 2024, neither Study SRP-9001-103 (ENDEAVOR) nor Study SRP-9001-301 (EMBARK) have been published in a peer-reviewed journal.

Micro-dystrophin as a Surrogate Biomarker

In preparation for its Cellular Tissue and Gene Therapy Advisory Committee meeting, the FDA issued a briefing document. The document noted that, “measurement of levels of Sarepta’s micro-dystrophin in muscle tissue only provides information about expression of the transgene product in cells transduced by ELEVIDYS, rather than insight into a pharmacologic effect on a biomarker in the pathway of the disease”. The FDA document cautioned that the wild-type (naturally occurring) dystrophin protein not only serves as a shock absorber, but may play an important scaffolding role and helps to recruit potassium, sodium and calcium channels as well as neuronal nitric oxide synthase (a protein known to play a role in the protection of muscle cells and in the control of local blood flow by antagonizing sympathetic vasoconstriction) and signaling proteins (for example, kinases). Sarepta’s abbreviated micro-dystrophin lacks key regions such as those binding neuronal nitric oxide synthase and alpha-syntrophin, and the areas that recruit signaling molecules and ion channels. Therefore, it is unclear to what extent Sarepta’s micro-dystrophin is functionally similar to wild-type dystrophin or to shortened forms of dystrophin in individuals with BMD (U.S. FDA 2023a).

FDA Cellular Tissue and Gene Therapy Advisory Committee Findings

On May 12, 2023, the FDA’s Advisory Committee was presented clinical evidence, including clinical testimony from providers, and patients with DMD and their families. The sponsor presented materials supporting the argument that the expression of ELEVIDYS in the participants’ cells was a reasonable endpoint likely to predict clinical benefit, that risks were monitorable and manageable, and that the totality of clinical evidence with appropriate clinical trial comparators was sufficient to support accelerated approval. The sponsor also reminded the committee that waiting for additional confirmatory data would guarantee additional muscle loss in children who might otherwise receive treatment. The available therapies that address the underlying cause of disease (four exon-skipping drugs) only treat a small percentage of individuals with DMD harboring specific gene mutations. At the conclusion of the meeting, the committee voted 8-6 to recommend accelerated approval.

The FDA approved the expanded indication on June 20, 2024, to include non-ambulatory individuals at least 4 years of age who have a mutation in their DMD gene. The expanded indication does not have an upper age limit. The decision memo from the director of FDA’s Center for Biologics Evaluation and Research (CBER) refers to evidence provided by Study 301 and Study 103 described above. While acknowledging that the primary endpoint in Study 301 (change in NSAA from baseline to week 52) did not show a statistically significant difference between treated individuals and controls, the director approved the manufacturer’s request for an expanded indication. The director cited changes in secondary outcomes as the basis for this decision. Of note, the trial was not designed to evaluate these secondary outcomes. These secondary outcome changes included a 0.64 second reduction in the time to rise from the floor (TTR) and a 0.42 meter/second increase in the 10 minute walk/run test (10MWR). The director cited data from Duong (2021) showing that the MCID for the TTR is 0.026 rise/s and, for the 10MWR, the MCID is 0.138 m/s.

CBER’s director issued these concluding statements:

> Overall, the demonstrated benefits of ELEVIDYS in the treatment of ambulatory individuals, and the expected benefits of ELEVIDYS in non-ambulatory individuals, with DMD over 4 years of age who are eligible to receive this therapy in improving key functional endpoints such as the ability to stand, walk, or climb stairs, outweigh the risks. The benefit to risk considerations are favorable taking into account the existing uncertainties, such as the ultimate duration of response. Although it might be argued that other gene therapy products in development may prove superior to ELEVIDYS in future clinical trials, these products have yet to receive regulatory approval. During this time, the availability of this gene therapy option may help slow or prevent irreversible decline that might otherwise occur in both ambulatory and non-ambulatory individuals, particularly since the latter have few or no alternative treatments available to address their imminent further decline in function over time (US FDA CBER, 2024)

In making this decision to approve the request for expanded indications, CBER’s director overruled the recommendation of the Office of Clinical Evaluation in their Office of Therapeutic Products (OCE-OTP) which had conducted FDA’s technology assessment for the request. CBER’s OCE-OTP director’s summary of that office’s evaluation included this statement:

> [T]he results of Study 301 do not constitute substantial evidence of effectiveness. The trial was designed to show a statistically significant difference in the mean change in NSAA total score from baseline to Week 52 in the intention-to-treat population. The study was designed in keeping with accepted standards for statistical rigor for regulatory purposes, with a less than 5% chance that the result would (falsely) show a difference (i.e., that the Elevidys group performed better or worse than the placebo group) when no difference exists, also known as Type 1 error. The Applicant conducted analyses of additional physical function outcome measures and also conducted analyses in age-defined subgroups in Study 301 without controlling for Type 1 error. Given the exploratory nature of these analyses, they are considered potentially hypothesis generating but the results do not constitute substantial evidence of

effectiveness due to the high likelihood that observed differences between the treatment groups may be due to chance.

The OCE-OTP director made the following recommendation regarding the request for expanded indications:

Specifically, it is my assessment that the data submitted in the sBLA:

- do not verify the clinical benefit of Elevidys in ambulatory boys aged 4-5 years (i.e., the group for which accelerated approval was granted by Center Director override of the review team and senior CBER leadership recommendation),
- do not demonstrate the benefit of Elevidys in ambulatory patients greater than age 5 years of age, or
- do not demonstrate the benefit of Elevidys in non-ambulatory patients of any age.

Potential Benefits, Risks, and Uncertainties of ELEVIDYS

The potential benefits of gene therapy for DMD include a delay in disease progression, greater life expectancy and improved quality of life. While the overall results from clinical trials (SRP-9001-102) show only a modest response to treatment in the younger age group (age 4-5), treating physicians and parents report cases of exceptional responses.

The administration of ELEVIDYS is not without risk and some uncertainties. In clinical studies, elevated liver function tests (including increases in GGT, GLDH, ALT, AST, or total bilirubin) were commonly reported within 8 weeks following ELEVIDYS infusion. The majority of cases were asymptomatic, and all cases resolved spontaneously or with systemic corticosteroids and resolved without clinical sequelae within 2 months. There were no reported cases of liver failure. Practitioners are advised to perform liver enzyme test prior to the administration of ELEVIDYS and to monitor liver function with clinical exam, total bilirubin and GGT weekly for the first 3 months following ELEVIDYS infusion.

In clinical trials, immune-mediated myositis was also observed approximately 1 month following ELEVIDYS infusion in participants with deletion mutations involving exon 8 and/or exon 9 in the DMD gene. Symptoms included severe muscle weakness, including dysphagia, dyspnea and hypophonia. In a life-threatening case of immune-mediated myositis, symptoms resolved during in-patient hospital care, and while muscle strength gradually improved, it did not return to baseline level. It is believed that these immune reactions may be due to a T-cell based response from lack of self-tolerance to a particular region encoded by the transgene corresponding to exons 1-17 of the DMD gene. Currently, there are limited data available for ELEVIDYS treatment in individuals with mutations in the DMD gene in exons 1 to 17 and/or exons 59 to 71. Individuals with deletions in these particular regions may be at risk for a severe immune-mediated myositis reaction. The product label cautions that ELEVIDYS is contraindicated in individuals with any deletion in exon 8 and/or exon 9 in the DMD gene due to the elevated risk for a severe immune-mediated myositis reaction.

Another uncertainty is the possibility that individuals who take the product may not be able to receive another more effective gene therapy using the same vector in the future. It is also unclear whether individual factors, such as age at treatment and severity of disease are predictive of response, or whether the treatment provides a long-term, durable benefit. Furthermore, muscle cell turnover is likely to dilute production of micro-dystrophin protein expression over time (Elangkovan, 2021).

Summary

DMD is a progressive and fatal condition. Gene therapy has the potential to delay disease progression for DMD with a single treatment, and possibly provide a durable cure. The available peer-reviewed, published literature on the use of ELEVIDYS as a gene therapy treatment for DMD is limited to a single phase I/IIa trial with four participants. Other data presented with the accelerated approval application demonstrated improvements in surrogate biomarkers. Clinical improvement was limited to a subgroup analysis of 4-5 year olds based on NSAA scores. The paucity of clinical data and the short follow-up period raises concerns. Nevertheless, the lack of any other effective treatment, DMD's inexorable and universally fatal course, promising results from a small number of treated 4-5-year-old boys, and the experience of some treating physicians and patients, makes it reasonable to offer treatment to that group while awaiting outcomes from larger trials and long-term follow-up.

While there are limited clinical data, sufficient scientific evidence permits reasonable conclusions that treatment with ELEVIDYS increases the expression of the ELEVIDYS micro-dystrophin protein in ambulatory individuals with DMD aged 4 to 5 years with a confirmed mutation in the DMD gene in a manner that appears likely to improve physical function and mobility.

At this time, there is insufficient credible evidence in the published peer-reviewed literature to demonstrate ELEVIDYS infusion improves net health outcomes for non-ambulatory individuals or for individuals outside of the 4 to 5 years age group.

Background/Overview

Duchenne Muscular Dystrophy

DMD is inherited in an X-linked recessive pattern, occurring almost exclusively in males, though females may infrequently be affected. DMD is completely penetrant in males. In heterozygous females, penetrance varies and may depend in part on patterns of X-chromosome inactivation. Approximately 30% of cases are due to new mutations and may occur in individuals who do not have a family history of DMD. DMD does not display a predilection for any race or ethnic group (Darras, 2022).

A diagnosis of DMD is made based upon a thorough clinical evaluation, a detailed patient history, and specialized tests including molecular genetic tests. Molecular genetic tests (frequently using blood or muscle cell samples) involve the examination of deoxyribonucleic acid (DNA) to identify single point mutations, deletions, or duplications. These techniques can also be used to diagnosis DMD prenatally. When genetic tests are not informative, tissue biopsy may reveal characteristic changes to muscle fibers. Creatine kinase testing can be used to confirm that muscle is inflamed or damaged, but cannot definitively diagnose DMD. Additionally, other techniques such as immunofluorescence, immunostaining, or Western blot (immunoblot) can be performed on muscle samples to identify the presence and levels of specific proteins within cells (Darras, 2022; NORD, 2016).

Standard therapies used to treat and manage DMD are aimed at the specific symptoms. Treatment options generally include physical therapy and active and passive exercise to build muscle strength and prevent contractures. Surgery may be recommended in select individuals to treat scoliosis or contractures. Braces may be employed to prevent the development of contractures. The use of mechanical aids (e.g., canes, braces, and wheelchairs) may be necessary to assist with ambulation. Corticosteroids may be used to slow the progression of muscle weakness in affected individuals and delay the loss of ambulation. Medications for cardiac function, as well as tracheostomy and assisted ventilation to support respiratory function may also be used (Darras, 2022; NORD, 2016).

More recently, the FDA approved the use of several exon skipping, disease-modifying treatments for a subset of individuals with specific DMD mutations. Exon skipping treatments allow the body to "skip over" errors in the dystrophin gene to make a shorter form of dystrophin. For example:

- Amondys 45 (casimersen) is indicated to treat individuals with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping (Amondys 45 2021).
- Exondys 51 (eteplirsen) injection is indicated for individuals who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping (Exondys 51, 2016).
- Viltepso (viltolarsen) and Vyondys 53 (golodirsen) are indicated to treat individuals with DMD who have a confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping (Viltepso, 2020; Vyondys 53, 2021).

For more information regarding disease-modifying and exon-skipping treatments for DMD (for example: casimersen [Amondys 45], viltolarsen [Viltepso], and golodirsen [Vyondys 53]), please refer to clinical pharmacy criteria.

Gene Therapy for DMD

Gene therapy, also known as gene replacement therapy, introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction. A gene may be altered using a “vector” or a “carrier” which is often a virus that has been modified to remove disease-causing genes, or DNA may be changed using genome (gene) editing, a group of technologies that allows genetic material to be added, removed, or altered. There are different approaches to gene therapy including replacing a mutated gene with a healthy gene, inactivating a mutated gene not functioning correctly, or introducing a new gene.

Gene therapy clinical trials for DMD are currently underway. On June 22, 2023, the FDA approved the use of delandistrogene moxeparvovec-rokl (ELEVIDYS) gene therapy for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene.

Definitions

Ambulatory: Able to walk, with or without an assistive device, such as a cane or walker (in contrast to “non-ambulatory”: unable to walk and requiring use of a wheelchair on a regular basis).

Adeno-associated virus (AAV): A small virus that infects humans and is not known to cause disease. Modified (non-replicating) AAVs are frequently used as viral vectors for gene therapy.

Becker muscular dystrophy (BMD): A type of muscular dystrophy that is similar to but not as severe as DMD. BMD has a later onset and milder symptoms than DMD but can affect the heart in a manner similar to DMD.

Cytoskeleton: A complex and dynamic network of proteins and filaments in the cytoplasm of many cells. The cytoplasm supplies structural support and transport for the cell and its parts.

Dystrophin: A protein that is required for muscles to function properly. This protein is missing or found in inadequate amounts in individuals with DMD.

Fibrosis: Thickening and scaring of tissue.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction; also known as gene therapy.

Handheld dynamometry: A small, portable device used to evaluate muscle strength.

North Star Ambulatory Assessment (NSAA): A 17-item rating scale that is frequently used in clinical trials to evaluate and measure motor function.

Phenotype: Observable traits or characteristics in an individual that result from having particular genes (in other words, genotype) and from the interaction of the genotype with the environment.

Sacrcolemma: The cell membrane that encases a skeletal muscle fiber, also referred to as the myolemma.

Surrogate endpoint: A marker, such as a physical sign, laboratory measurement, or radiographic image or biomarker that is “reasonably likely” to predict clinical benefit, but in and of itself does not measure clinical benefit (such as changes in survival or symptoms).

Transgene: A gene that is removed from one organism and transferred to another. The transgene consists of a segment of DNA which contains instructions for the production of a specific functional protein.

X-linked recessive trait: A mutation in the gene on the X-chromosome. The phenotype is always expressed in males (who have only one X chromosome) and in females who have mutations in both of their X chromosomes.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS

J1413	Injection, delandistrogene moxeparvovec-rokl, per therapeutic dose [ELEVIDYS]

ICD-10 Diagnosis

G71.01	Duchenne or Becker muscular dystrophy

When services are Investigational and Not Medically Necessary:
For the procedure code listed above when criteria are not met or for all other diagnoses not listed.

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Government Agency, Medical Society, and Other Authoritative Publications:

1. Amondys 45 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; Last updated February 2021. Available at: Amondys 45 (casimersen) Label (fda.gov). Accessed on August 10, 2023.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: https://clinicaltrials.gov/ct2/home. Accessed on July 23, 2024.
    a. A gene transfer therapy study to evaluate the safety and efficacy of SRP-9001 (Delandistrogene Moxeparvovec) in participants with Duchenne muscular dystrophy (DMD) (EMBARK). NCT05096221. Available at: NCT05096221. Accessed on July 23, 2024.
    b. A gene transfer therapy study to evaluate the safety of and expression from SRP-9001 (Delandistrogene Moxeparvovec) in participants with Duchenne muscular dystrophy (DMD) (ENDEAVOR). NCT04626674. Available at: NCT04626674. Accessed on July 23, 2024.
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Websites for Additional Information

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC). Revised wording in the INV/NMN statement to include the brand name “(ELEVIDYS)” and remove the phrase “for all other indications, including”. Updated Rationale, Background/Overview, References and Websites for Additional Information sections. Revised Coding section to remove NOC codes C9399, J3490, J3590.
	12/28/2023	Updated Coding section with 01/01/2024 HCPCS changes, added J1413 replacing NOC codes for ELEVIDYS.
New	08/10/2023	MPTAC. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy,

should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.