



(<https://www.aetna.com/>)

Gene-Based Therapy for Duchenne Muscular Dystrophy (DMD)

[Clinical Policy Bulletins](#) | [Medical Clinical Policy Bulletins](#)

Number: 0911

Table Of Contents

[Policy](#)

[Applicable CPT / HCPCS / ICD-10 Codes](#)

[Background](#)

[References](#)

Policy History

[Last Review](#) 11/25/2024

Effective: 12/02/2016

Next Review: 05/22/2025

[Review History](#)

[Definitions](#)

Policy

Scope of Policy

This Clinical Policy Bulletin addresses gene-based therapy for Duchenne muscular dystrophy (DMD) for commercial medical plans. For Medicare criteria, see [Medicare Part B Criteria](#) (<https://www.aetna.com/health-care-professionals/medicare/part-b-step.html>).

Note: Requires Precertification:

Precertification of casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys), eteplirsen (Exondys 51), golodirsen (Vyondys 53), or viltolarsen (Viltepso) is required of all Aetna participating providers and members in applicable plan designs. For precertification of these medications, call (866) 752-7021 or fax (888) 267-3277. For Statement of Medical Necessity (SMN) precertification forms, see [Specialty Pharmacy Precertification](#) (<https://www.aetna.com/health-care-professionals/health-care-professional-forms.html>).

Note: Site of Care Utilization Management Policy applies to Amondys 45, Exondys 51, Vyondys 53, or Viltepso infusions, see [Utilization Management Policy on Site of Care for Specialty Drug Infusions](#) (<https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html>).

Note: For Elevidys, unless member's health plan has elected not to require, gene and cellular therapies must be administered at an Aetna Institutes® Gene Based, Cellular and Other Innovative Therapy (GCIT®) Network. For Elevidys, see [Aetna Institutes® GCIT Designated Centers](#) (<https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html>).

Additional Information

[Clinical Policy Bulletin Notes](#)

A. Prescribing Specialties

This medication must be prescribed by or in consultation with a physician who specializes in treatment of Duchenne muscular dystrophy (DMD).

B. Criteria for Initial Approval

Aetna considers casimersen (Amondys 45) medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all of the following criteria are met:

1. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation; and
2. The DMD gene mutation is amenable to exon 45 skipping (refer to examples in Appendix A); and
3. Treatment with Amondys 45 is initiated before the age of 14; and
4. Member is able to achieve an average distance of at least 300 meters while walking independently over 6 minutes; and
5. Member meets one of the following criteria:
 - a. Member has not previously received gene replacement therapy for DMD (e.g., Elevidys); or
 - b. Member has previously received gene replacement therapy for DMD (e.g., Elevidys) and has experienced a worsening in clinical status since receiving gene replacement therapy (e.g., decline in ambulatory function); and
6. Member will not exceed a dose of 30 mg/kg once weekly.

Aetna considers all other indications as experimental, investigational, or unproven.

C. Continuation of Therapy

Note: Members who were previously established on Amondys 45 and subsequently administered gene replacement therapy (e.g., Elevidys) must meet all initial criteria prior to re-starting Amondys 45.

Aetna considers continuation of casimersen (Amondys 45) therapy medically necessary for DMD when both of the following criteria are met:

1. The member has demonstrated a response to therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent); and
2. The member will not exceed a dose of 30 mg/kg once weekly.

II. Delandistrogene Moxeparvovec-rokl (Elevidys)

A. Exclusions

1. Coverage will not be provided for members with a deletion in exon 8 and/or exon 9 in the DMD gene;
2. Elevidys will not be used in combination with exon-skipping therapies (e.g., casimersen, eteplirsen, golodirsen, viltolarsen).

B. Prescriber Specialties

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD) (e.g., pediatric neurologist, neuromuscular specialist).

C. Criteria for Initial Approval

Aetna considers one dose total of delandistrogene moxeparovovec-rokl (Elevidys) medically necessary for treatment of Duchenne muscular dystrophy (DMD) when all of the following criteria are met:

1. Member is male; and
2. Member is 4 - 20 years of age; and
3. Member has a definitive diagnosis of DMD confirmed via genetic testing; and
4. Member meets either of the following criteria:
 - a. Member is ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent); or
 - b. Member is non-ambulatory and has a Performance Upper Limb (PUL) entry item score of at least 3 and a total PUL score of 20 - 40; and
5. Member has anti-recombinant adeno-associated virus serotype rh74 (anti-AAVrh74) total binding antibody titers of less than 1:400; and
6. Member does not currently have an active infection; and
7. Member has been on a stable dose of corticosteroids (e.g., prednisone) for at least 12 weeks prior to and following receipt of Elevidys infusion unless contraindicated or not tolerated; and
8. Member does not have signs of cardiomyopathy (e.g., ejection fraction less than 40%); and
9. Liver function, platelet count, and troponin-I levels have been assessed at baseline and will be monitored as clinically appropriate; and
10. Member has not received treatment with Elevidys previously.

Aetna considers all other indications as experimental, investigational, or unproven.

III. Eteplirsen (Exondys 51)

A. Prescriber Specialties

This medication must be prescribed by or in consultation with a physician who specializes in treatment of Duchenne muscular dystrophy (DMD).

B. Criteria for Initial Approval

Aetna considers eteplirsen (Exondys 51) injection medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all of the following criteria are met:

1. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation; and
2. The DMD gene mutation is amenable to exon 51 skipping (refer to examples in Appendix B); and
3. Treatment with Exondys 51 is initiated before the age of 14; and
4. Member is able to achieve an average distance of at least 180 meters while walking independently over 6 minutes; and
5. Member meets one of the following criteria:
 - a. Member has not previously received gene replacement therapy for DMD (e.g., Elevidys); or
 - b. Member has previously received gene replacement therapy for DMD (e.g., Elevidys) and has experienced a worsening in clinical status since receiving gene replacement therapy (e.g., decline in ambulatory function); and
6. Member will not exceed a dose of 30 mg/kg.

Aetna considers all other indications as experimental, investigational, or unproven.

C. Continuation of Therapy

Note: Members who were previously established on Exondys 51 and subsequently administered gene replacement therapy (e.g., Elevidys) must meet all initial criteria prior to re-starting Exondys 51.

Aetna considers continuation of eteplirsen (Exondys 51) therapy medically necessary for members with DMD when both of the following criteria are met:

1. The member has demonstrated a documented response to therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent); and
2. The member will not exceed a dose of 30 mg/kg.

IV. Golodirsen (Vyondys 53)

A. Prescriber Specialties

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

B. Criteria for Initial Approval

Aetna considers golodirsen (Vyondys 53) injection medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all of the following criteria are met:

1. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation; and
2. The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix C); and
3. Treatment with Vyondys 53 is initiated before the age of 16; and
4. Member is able to achieve an average distance of at least 250 meters while walking independently over 6 minutes; and
5. Member meets one of the following criteria:
 - a. Member has not previously received gene replacement therapy for DMD (e.g., Elevidys); or
 - b. Member has previously received gene replacement therapy for DMD (e.g., Elevidys) and has experienced a worsening in clinical status since receiving gene replacement therapy (e.g., decline in ambulatory function); and
6. Member will not exceed a dose of 30 mg/kg; and
7. The requested medication will not be used concomitantly with vitolarsen.

Aetna considers all other indications as experimental, investigational, or unproven.

C. Continuation of Therapy

Note: Members who were previously established on Vyondys 53 and subsequently administered gene replacement therapy (e.g., Elevidys) must meet all initial criteria prior to re-starting Vyondys 53.

Aetna considers continuation of golodirsen (Vyondys 53) therapy medically necessary for members with DMD when all of the following criteria are met:

1. The member has demonstrated a documented response to therapy as evidence by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent); and

2. The member will not exceed a dose of 30 mg/kg; and
3. The requested medication will not be used concomitantly with viltolarsen.

V. Viltolarsen (Viltepso)

A. Prescriber Specialties

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

B. Criteria for Initial Approval

Aetna considers viltolarsen (Viltepso) medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all of the following criteria are met:

1. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation; and
2. The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix C); and
3. Treatment with Viltepso is initiated before the age of 10; and
4. Member is able to walk independently without assistive devices; and
5. Member meets one of the following criteria:
 - a. Member has not previously received gene replacement therapy for DMD (e.g., Elevidys); or
 - b. Member has previously received gene replacement therapy for DMD (e.g., Elevidys) and has experienced a worsening in clinical status since receiving gene replacement therapy (e.g., decline in ambulatory function); and
6. Member will not exceed a dose of 80 mg/kg; and
7. The requested medication will not be used concomitantly with golodirsen.

Aetna considers all other indications as experimental, investigational, or unproven.

C. Continuation of Therapy

Note: Members who were previously established on Viltepso and subsequently administered gene replacement therapy (e.g., Elevidys) must meet all initial criteria prior to re-starting Viltepso.

Aetna considers viltolarsen (Viltepso) therapy medically necessary for members requesting continuation of therapy when all of the following criteria are met:

1. The member has demonstrated a documented response to therapy as evidenced by remaining ambulatory (e.g., not wheelchair dependent); and
2. The member will not exceed a dose of 80 mg/kg; and
3. The requested medication will not be used concomitantly with golodirsen.

Note: Lab results from genetic testing are a required component of clinical documentation for precertification review.

VI. Related Policies

For givinostat (Duvyzat) oral suspension in Duvyzat 6437-A SGM*, refer to pharmacy benefit plan.

For vamorolone (Agamree) oral suspension in Agamree 6225-A SGM*, refer to pharmacy benefit plan.

Dosage and Administration

Casimersen (Amondys 45)

Casimersen is available as Amondys 45 for injection as 100 mg/2 mL in a single-dose vial for intravenous infusion.

The recommended dosage of Amondys 45 is 30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous infusion via an in-line 0.2 micron filter. If a dose of Amondys 45 is missed, it may be administered as soon as possible after the scheduled dose.

Source: Sarepta Therapeutics, 2023

Delandistrogene Moxeparvovec-rokl (Elevidys)

Delandistrogene moxeparvovec-rokl is available as Elevidys and is supplied as a suspension with a nominal concentration of 1.33×10^{13} vector genomes per milliliter (vg/mL) for use as a single-dose intravenous infusion only. Elevidys is provided in a customized kit containing ten to seventy 10 mL single-dose vials, with each kit constituting a dosage unit based on the individual's body weight.

Recommended dosage for persons 10 to less than 70 kg: 1.33×10^{14} vector genomes (vg) per kg of body weight; 70 kg or greater: 9.31×10^{15} vg total fixed dose. There is limited safety data available in non-ambulatory persons weighing 70 kg or greater, who received the maximum dose of Elevidys, 9.31×10^{15} vg, in clinical trials.

Elevidys administration is not recommended in persons with elevated anti-AAVrh74 total binding antibody titers ($\geq 1:400$). Re-administration of Elevidy is not recommended.

Source: Sarepta Therapeutics, 2024

Eteplirsen (Exondys 51)

Eteplirsen is available as Exondys 51 for injection as 100 mg/2 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL) in single-dose vials for intravenous infusion.

The recommended dose of Exondys 51 is 30 mg/kg administered once weekly as a 35 to 60-minute intravenous infusion. If a dose of Exondys 51 is missed, it may be administered as soon as possible after the scheduled time.

Source: Sarepta Therapeutics, 2022

Golodirsen (Vyondys 53)

Golodirsen is available as Vyondys 53 for injection as 100 mg/2 mL (50 mg/mL) in a single-dose vial for intravenous infusion.

The recommended dose of Vyondys 53 is 30 mg/kg administered once weekly as a 35 to 60-minute intravenous infusion. If a dose of Vyondys 53 is missed, it may be administered as soon as possible after the scheduled dose.

Source: Sarepta Therapeutics, 2021b

Viltolarsen (Viltepso)

Viltolarsen is available as Viltepso for injection and supplied as 250 mg/5 mL (50 mg/mL) in a single-dose vial for intravenous infusion.

The recommended dosage of Viltepso is 80 mg/kg of body weight administered once weekly as a 60-minute intravenous infusion. If a dose of Viltepso is missed, it should be administered as soon as possible after the scheduled dose time.

Note: Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting Viltepso.

Source: NS Pharma, 2021

CPT Codes / HCPCS Codes / ICD-10 Codes

Other CPT codes related to the CPB:

Code	Code Description
96365 - 96368	Intravenous infusion, for therapy, prophylaxis or diagnosis
96369 - 96372	Subcutaneous infusion, for therapy or prophylaxis
96379	Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion

HCPCS codes covered if selection criteria are met:

J1413	Injection, delandistrogene moxeparovovec-rokl, per therapeutic dose
J1426	Injection, casimersen, 10 mg
J1427	Injection, viltolarsen, 10 mg
J1428	Injection, eteplirsen, 10 mg
J1429	Injection, golodirsen, 10 mg

Other HCPCS codes related to the CPB:

J0702	Injection, betamethasone acetate 3mg and betamethasone sodium phosphate 3mg
J1020	Injection, methylprednisolone acetate, 20 mg
J1030	Injection, methylprednisolone acetate, 40 mg
J1040	Injection, methylprednisolone acetate, 80 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J2920	Injection, methylprednisolone sodium succinate, up to 40 mg
J2930	Injection, methylprednisolone sodium succinate, up to 125 mg
J7509	Methylprednisolone oral, per 4 mg
J7510	Prednisolone oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg

ICD-10 codes covered if selection criteria are met:

G71.01	Duchenne or Becker muscular dystrophy
--------	---------------------------------------

Background

Duchenne muscular dystrophy (DMD) is a rare genetic condition characterized by progressive muscle deterioration and weakness of skeletal and heart muscles. DMD is the most common childhood onset form of muscular dystrophy which primarily affects males, though in rare cases may affect females. DMD is estimated to occur in about 16 live male births per 100,000 in the USA (NIH, 2020). The first symptoms are usually seen between three and five years of age and worsen over time. DMD is caused by DNA variants in the *DMD* gene and is inherited in an X-linked recessive pattern. The condition may occur in people who do not have a family history of DMD. There is no known cure for DMD. Treatment is targeted at controlling symptoms and related complications caused by severe progressive muscle weakness and loss. Medications (such as steroids) may improve the strength and function of muscles. Additional medications are available for people with DMD with a specific DNA variant (FDA, 2020; NIH, 2020).

Duchenne muscular dystrophy (DMD) is caused mainly by internal deletions in the gene for dystrophin, a protein essential for maintaining muscle cell membrane integrity. These deletions abrogate the reading frame and the lack of dystrophin results in progressive muscle deterioration. Patients with DMD experience progressive loss of ambulation, followed by a need for assisted ventilation, and eventual death in mid-20s. By the method of exon skipping in dystrophin pre-mRNA the reading frame is restored and the internally deleted but functional dystrophin is produced (Kole and Krieg, 2015). There are oligonucleotide drugs available that induce desired exon skipping for persons with DMD.

Casimersen (Amondys 45)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Amondys 45 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Casimersen is available as Amondys 45 (Sarepta Therapeutics, Inc.), which is an antisense oligonucleotide. Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping.

Amondys 45 carries labeled warnings and precautions for risk of hypersensitivity reactions, including angioedema and anaphylaxis, which have occurred in patients receiving Amondys 45 therapy. Moreover, kidney toxicity was observed based on animal data. Although kidney toxicity was not observed in the clinical studies for casimersen, kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Thus, kidney function should be monitored in patients taking Amondys 45. Creatinine may not be a reliable measure of renal function in DMD patients.

The most common adverse reactions (incidence greater than 20% and at least 5% higher than placebo) include upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain.

In February 2021, the U.S. FDA granted accelerated approval of Amondys 45 for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed mutation amenable to exon 45 skipping. The approval under accelerated review was based on an increase in dystrophin production in skeletal muscle of patients amenable to exon 45 skipping from the ESSENCE trial. Continued approval may be contingent upon verification of a clinical benefit in confirmatory trials.

The ESSENCE trial an ongoing, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of casimersen and golodirsen in ambulatory patients with DMD with mutations amendable to exon 45 or 53 skipping. For the casimersen segment, the study is planned to enroll a total of 111 patients, age 7 to 13 years, randomized to casimersen or placebo in a 2 to 1 ratio. Patients were required to have confirmed DMD with genetic deletion amendable to exon 45, been on a stable dose of oral corticosteroids for at least 24 weeks prior to dosing with casimersen or placebo, and have a mean 6 minute-walk-test (MWT) greater than or equal 300 meters and less than or equal to 450 meters. Following the 96-week double-blind period, all patients began or are to begin an additional 48 week open-label treatment period. Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48. Interim results from 43 evaluable patients (n = 27, casimersen; n = 16, placebo) who had a muscle biopsy at Week 48 of the double-blind period found change from baseline mean (SD) of 0.81 (0.70) for the casimersen study arm, and 0.22 (0.49) for placebo. The ESSENCE trial is expected to conclude in 2024 (Sarepta, 2020, 2021a, 2023a).

Delandistrogene Moxeparvovec-rokl (Elevidys)

U.S. Food and Drug Administration (FDA)-Approved Indications

■ Elevidys is indicated in individuals at least 4 years of age:

- For the treatment of Duchenne muscular dystrophy (DMD) in patients who are ambulatory and have a confirmed mutation in the DMD gene;
- For the treatment of DMD in patients who are non-ambulatory and have a confirmed mutation in the DMD gene**.

**The DMD indication in non-ambulatory patients is approved under accelerated approval based on expression of Elevidys microdystrophin. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Delandistrogene moxeparvovec-rokl, an adeno-associated virus vector-based gene therapy, is available as Elevidys (Sarepta Therapeutics, Inc.). Elevidys is a recombinant gene therapy that targets a genetic cause of Duchenne, mutations in the dystrophin gene that result in the lack of dystrophin protein, by delivering a gene that codes for a shortened form of dystrophin to muscle cells known as Elevidys micro-dystrophin. Specifically, Elevidys is comprised of a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) capsid and a single-stranded DNA expression cassette flanked by inverted terminal repeats (ITRs) derived from AAV2. The cassette contains: (i) an MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α -myosin heavy chain enhancer, and (ii) the DNA transgene encoding the engineered micro-dystrophin protein.

In 2023, Elevidys was FDA-approved, through the FDA's Accelerated Approval pathway, as a single-dose gene transfer therapy for intravenous infusion designed to address the underlying cause of DMD through the targeted production of Elevidys micro-dystrophin in skeletal muscle.

FDA approval was based on data from an ongoing multi-center study (Study 1) that was derived of two parts, a 48-week randomized, double-blind, placebo-controlled period, followed by a 48-week period in which patients who received placebo during part 1 of the study were treated with Elevidys, and patients who received Elevidys received a placebo. The study includes 41 DMD patients aged 4 through 7 years with either a confirmed mutation, or a premature stop codon mutation between exons 18 to 58 in the DMD gene. Patients were randomized 1:1 to receive either Elevidys (n=20) or placebo (n=21), as a single intravenous infusion via a peripheral limb. Randomization was stratified by age (i.e., aged 4 to 5 years vs. aged 6 to 7 years). In the Elevidys group, 8 patients received 1.33×10^{14} vg/kg of delandistrogene moxeparvovec-rokl, and 12 patients received lower doses. All randomized patients had baseline anti-AAVrh74 antibody titers less than 1:400. The primary objectives of the study were to evaluate expression of Elevidys micro-dystrophin in skeletal muscle, and to evaluate the effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score, which was assessed from baseline to Week 48 after infusion of Elevidys or placebo. The difference between the Elevidys and placebo groups was not statistically significant ($p=0.37$). However, the exploratory subgroup analyses showed that for patients aged 4 through 5 years, the least squares (LS) mean changes (standard error [SE]) in NSAA total score from baseline to Week 48 were 4.3 (0.7) points for the Elevidys group, and 1.9 (0.7) points for the placebo group, a numerical advantage for Elevidys. For patients aged 6 through 7 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) points for the Elevidys group and 0.5 (0.7) points for the placebo group, a numerical disadvantage for Elevidys.

Study 2 is an ongoing, open-label, multi-center trial which includes a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years. All 20 patients have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the DMD gene. All patients had baseline anti-AAVrh74 antibodies titers less than 1:400 (as determined by the investigational total binding antibody ELISA) and received a single intravenous infusion of 1.33×10^{14} vg/kg Elevidys. The primary objective of the study was to evaluate the effect of Elevidys micro-dystrophin expression as measured by western blot. For patients aged 4 through 5 years who received 1.33×10^{14} vg/kg of Elevidys, the mean (SD) Elevidys micro-dystrophin expression levels (change from baseline) at Week 12 following Elevidys infusion were 95.7% (n=3, SD: 17.9%) in Study 1 Parts 1 and 2 and 51.7% (n=11, SD: 41.0%) in Study 2 Cohort 1. Change from baseline was statistically significant.

The FDA concluded that the data submitted demonstrated that an increase in this surrogate endpoint (expression of Elevidys micro-dystrophin) is reasonably likely to predict clinical benefit in persons 4 to 5 years of age with DMD who do not have significant pre-existing antibody titers against the AAV rh74 vector or have other contraindications based on the inclusion criteria of the clinical trials. However, a clinical benefit of Elevidys, including improved motor function, has not been established. As a condition of approval, the FDA is requiring Sarepta Therapeutics to complete a clinical study to confirm Elevidys' clinical benefit. The required study is designed to assess whether Elevidys improves physical function and mobility in ambulatory DMD patients with a confirmed mutation in the DMD gene (FDA, 2023). Thus, the EMBARK trial, a global, randomized, double-blind, placebo-controlled Phase 3 trial for Elevidys, will serve as the post-marketing confirmatory trial and is fully enrolled with results expected in late 2023.

Study 3 is a multi-center, randomized, double-blind, placebo-controlled trial in which Elevidys was evaluated in 125 (Elevidys, n=63; placebo, n=62) ambulatory male patients 4 to 7 years of age with a confirmed frameshift, splice site, premature stop codon, or disease-causing mutation in the *DMD* gene starting at or after exon 18. All patients had baseline anti-AAVrh74 antibodies titers less than 1:400 as determined by the investigational total binding antibody ELISA and received a

single intravenous infusion of 1.33×10^{14} vg/kg Elevidys. The efficacy outcome measure was to evaluate the effect of Elevidys on physical function as assessed by the NSAA total score. Key secondary outcome measures were to evaluate expression of micro-dystrophin in skeletal muscle, time to rise from floor, and time of 10-meter walk/run. Additional efficacy outcome measures included time of 100-meter walk/run, and time to ascend 4 steps. The change in NSAA total score was assessed from baseline to Week 52 after infusion of Elevidys (n=63) or placebo (n=61) in which the difference between the groups were not statistically significant ($p=0.24$). The least squares (LS) mean changes in NSAA total score from baseline to Week 52 was 2.57 (95% confidence interval [CI]: 1.80, 3.34) points for the Elevidys group and 1.92 (95% CI: 1.14, 2.70) points for the placebo group, with a LS mean difference from placebo of 0.65 (95% CI: -0.45, 1.74). Changes of clinical relevance were noted in three secondary efficacy endpoints, including time to rise from the floor, 10-meter walk/run and time to ascend 4 steps.

In June 2024, the FDA approved a label expansion to include individuals who are at least 4 years of age diagnosed with DMD who have confirmed mutation in the *DMD* gene. Elevidys was previously approved under accelerated approval for ambulatory individuals 4 through 5 years of age with DMD with a confirmed mutation in the *DMD* gene. Confirming the functional benefits, the FDA granted traditional approval for ambulatory patients. Moreover, the FDA granted accelerated approval for non-ambulatory patients. Continued approval for non-ambulatory Duchenne patients may be contingent upon verification of clinical benefit in a confirmatory trial. Elevidys remains contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.

FDA approval was based on clinical studies that evaluated the safety and efficacy of Elevidys. The efficacy was evaluated in two double-blind, placebo-controlled studies and two open-label studies, which enrolled a total of 218 male patients (including those who received placebo) with a confirmed disease-causing mutation in the *DMD* gene. "In one of the studies, the efficacy outcome measures were to evaluate expression of micro-dystrophin in skeletal muscle, and to evaluate the effect of Elevidys on the total score of patients on the North Star Ambulatory Assessment (NSAA). In another study, the primary efficacy outcome measure was to evaluate the effect of Elevidys on physical function as assessed by the NSAA total score. Key secondary outcome measures were to evaluate expression of micro-dystrophin in skeletal muscle, time to rise from floor and time of 10-meter walk/run. Additional efficacy outcome measures included time of 100-meter walk/run and time to ascend four steps. While the large, randomized study of Elevidys failed to meet its statistical primary endpoint of improvement versus placebo in the NSAA, the FDA found the observations regarding the secondary endpoints and exploratory endpoints to be compelling and to indicate clinical benefit compared to placebo. These endpoints include improvements in time to rise from the floor, 10-meter walk/run, time to ascend four steps and creatine kinase levels. Based on the totality of the evidence, the FDA determined the available evidence verifies the product's clinical benefit for its original indication, which was initially approved in June 2023 under accelerated approval, and provides substantial evidence of effectiveness to support traditional approval of Elevidys in ambulatory individuals 4 years of age and older with a confirmed mutation in the *DMD* gene except in those with any deletion in exon 8 and/or exon 9 in the *DMD* gene, in whom its use is contraindicated. An inadequate amount of safety data is available currently to support the use of Elevidys in individuals under 4 years of age" (FDA, 2024).

"In granting accelerated approval for non-ambulatory individuals aged 4 and older, the FDA considered the totality of the evidence, including clinical data in ambulatory individuals from a study in 4- to 7-year-olds, as well as from a study in 4- to 5-year-olds indicating a correlation of Elevidys micro-dystrophin levels with clinical outcome measures. Based on the evidence and given that the mechanism of action of Elevidys is similar for ambulatory and non-ambulatory populations, the

FDA determined that increased levels in micro-dystrophin is reasonably likely to predict clinical benefit in the non-ambulatory population. This conclusion, along with the evidence that Elevidys elevates micro-dystrophin levels, provides substantial evidence of effectiveness to support accelerated approval in non-ambulatory individuals at least 4 years of age with DMD considering the serious nature of the disease and the extent of unmet medical need in this group of individuals. A confirmatory randomized, controlled clinical trial in the non-ambulatory population is currently underway" (FDA, 2024).

The safety of Elevidys was established based on evaluation of 156 male patients with a confirmed mutation of the DMD gene who received Elevidys in four clinical studies, including one completed open-label study, one ongoing open-label study, and two studies that included a double-blind, placebo-controlled period. No new safety concerns appear to have been identified in the population of ambulatory individuals treated with the marketed product. A modest amount of safety data on non-ambulatory individuals was submitted to the FDA in the context of an ongoing randomized clinical trial; safety data in non-ambulatory individuals is limited, given the number of non-ambulatory individuals included in the trial and treated with the marketed product to date (FDA, 2024).

Elevidys is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.

Per the label, Elevidys should be postponed in patients with concurrent infections until the infection has resolved. Healthcare providers should assess liver function, platelet counts and troponin-I before infusion. One day prior to infusion, corticosteroid regimen is to be initiated for a minimum of 60 days. It is recommended to modify corticosteroid dose for patients with liver function abnormalities.

Elevidys carries labeled warning and precautions for infusion-related reactions, acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74. Infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during or up to several hours following Elevidys administration. In addition, administration of Elevidys may result in elevations of liver enzymes (e.g., GGT, ALT) and total bilirubin, typically seen within 8 weeks. In clinical trials, immune-mediated myositis was observed approximately 1 month following infusion in patients with deletion mutations involving exon 8 and/or exon 9 in the DMD gene. Symptoms of severe muscle weakness, including dysphagia, dyspnea and hypophonia, were observed. Limited data are available in patients with mutations in the DMD gene in exons 1 to 17 and/or exons 59 to 71. Patients with deletions in these regions may be at risk for a severe immune-mediated myositis reaction. Acute serious myocarditis and troponin-I elevations have been observed following Elevidys infusion in clinical trials. In AAV-vector based gene therapies, preexisting anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with Elevidys all subjects developed anti-AAVrh74 antibodies. Per the label, perform baseline testing for the presence of anti-AAVrh74 total binding antibodies prior to Elevidys administration. Elevidys administration is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers ($\geq 1:400$).

Elevidys is not intended for use in pregnant women, and there is no information available on the presence of Elevidys in human milk or its effects on the breastfed infant.

The most common adverse reactions across studies (incidence 5% or more) were vomiting and nausea, liver injury, pyrexia, and thrombocytopenia.

- Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Eteplirsen is available as Exondys 51 (Sarepta Therapeutics, Inc.), which is an antisense oligonucleotide. Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in clinical trials (Sarepta, 2022).

Exondys 51 includes labeled warnings and precautions for hypersensitivity reactions, including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension. The most common adverse reactions (incidence 35% or more and higher than placebo) include balance disorder and vomiting (Sarepta, 2022).

Mendell and colleagues (2013) noted that in prior open-label studies, eteplirsen, a phosphorodiamidate morpholino oligomer, enabled dystrophin production in DMD with genetic mutations amenable to skipping exon 51. The present study used a double-blind, placebo-controlled protocol to examine eteplirsen's ability to induce dystrophin production and improve distance walked on the 6-minute walk test (6MWT). Boys with DMD aged 7 to 13 years, with confirmed deletions correctable by skipping exon 51 and ability to walk 200 to 400 m on 6 MWT, were randomized to weekly intravenous infusions of 30 or 50 mg/kg/week eteplirsen or placebo for 24 weeks ($n = 4$ /group). Placebo patients switched to 30 or 50 mg/kg eteplirsen ($n = 2$ /group) at week 25; treatment was open label thereafter. All patients had muscle biopsies at baseline and week 48; effectiveness included dystrophin-positive fibers and distance walked on the 6MWT. At week 24, the 30 mg/kg eteplirsen patients were biopsied, and percentage of dystrophin-positive fibers was increased to 23 % of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$).

Even greater increases occurred at week 48 (52 % and 43 % in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma. Ambulation-evaluable eteplirsen-treated patients experienced a 67.3 m benefit compared to placebo/delayed patients ($p \leq 0.001$). The authors concluded that eteplirsen restored dystrophin in the 30 and 50 mg/kg/week cohorts, and in subsequently treated, placebo-controlled subjects. Duration, more than dose, accounted for dystrophin production, also resulting in ambulation stability. No severe adverse events (AEs) were encountered.

Mendell and associates (2016) continued evaluation of the long-term safety and effectiveness of eteplirsen in patients with DMD: 3-year progression of eteplirsen-treated patients was compared to matched historical controls (HC). Ambulatory DMD patients who were greater than or equal to 7 years old and amenable to exon 51 skipping were randomized to eteplirsen (30/50mg/kg) or placebo for 24 weeks. Thereafter, all received eteplirsen on an open-label basis. The primary functional assessment in this study was the 6MWT. Respiratory muscle function was assessed by pulmonary function testing (PFT). Longitudinal natural history data were used for comparative analysis of 6MWT performance at baseline and months 12, 24, and 36. Patients were matched to the eteplirsen group based on age, corticosteroid

use, and genotype. At 36 months, eteplirsen-treated patients (n = 12) demonstrated a statistically significant advantage of 151 m (p < 0.01) on 6MWT and experienced a lower incidence of loss of ambulation in comparison to matched HC (n = 13) amenable to exon 51 skipping. Results of PFT remained relatively stable in eteplirsen-treated patients. Eteplirsen was well-tolerated. Analysis of HC confirmed the previously observed change in disease trajectory at age 7 years, and more severe progression was observed in patients with mutations amenable to exon skipping than in those not amenable. The subset of patients amenable to exon 51 skipping showed a more severe disease course than those amenable to any exon skipping. The authors concluded that over 3 years of follow-up, eteplirsen-treated patients showed a slower rate of decline in ambulation assessed by 6MWT compared to untreated matched HC.

An UpToDate review on "Treatment of Duchenne and Becker muscular dystrophy" (Darras, 2016) states that "Results from small clinical studies in humans suggest the promise of this approach [gene therapy]. A small open-label study found that weekly intravenous administration of the exon 51 skipping drug eteplirsen induced a dose-related increase in dystrophin production without drug-related adverse effects. In a 24-week placebo-controlled trial with 12 patients, those assigned to the higher dose drug eteplirsen (50 mg/kg daily intravenously) showed a statistically significant improvement in the six-minute walk test. Findings from an open-label extension phase of the study through 36 months suggested that, compared with historical controls, eteplirsen-treated patients had continued benefit on the six-minute walk test and a lower rate of loss of ambulation".

On September 19, 2016, the Food and Drug Administration (FDA) granted accelerated approval to Exondys 51 (eteplirsen) injection -- the first drug approved to treat patients with Duchenne muscular dystrophy (DMD). Exondys 51 is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 % of the population with DMD. The pivotal clinical trial of eteplirsen for FDA approval included children under 14 years of age at study entry. The accelerated approval of Exondys 51 was based on the surrogate end-point of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients. The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. The most common AEs reported by subjects taking Exondys 51 in the clinical trials were balance disorder and vomiting. A clinical benefit of Exondys 51, including improved motor function, has not been established. In making the decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy. Under the accelerated approval provisions, the FDA is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The required study is designed to examine if Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

In a pooled analysis, Randeree and Eslick (2018) analyzed the results of previous studies to evaluate the safety and efficacy of eteplirsen. A literature search of electronic databases was performed. Only human studies using eteplirsen were eligible. A total of 4 relevant clinical studies were identified. A pooled-analysis was performed using data relating to percentage dystrophin-positive fibers obtained from muscle biopsy, and the 6 MWT. The average increase in percentage dystrophin-positive fibers after treatment with eteplirsen was 24.23 % (range of -4 to 78; SD 24.44 %). The average rate of decline in distance walked was 65 meters

(range of -335 to 83; SD 100.08 m). The authors concluded that whether or not this increase in percentage dystrophin-positive fibers and distance walked was clinically significant was unclear, and there is therefore a need for more clinical trials.

Shimizu-Motohashi and associates (2018) stated that exon skipping has been considered a promising therapeutic approach for DMD. Eteplirsen received conditional approval in the U.S. in 2016. To-date, no systematic reviews or meta-analyses of randomized controlled trials (RCTs) of exon skipping drugs have been published to determine the pooled estimates for the effect of exon skipping in treating DMD. These investigators carried out a systematic review and meta-analysis of double-blind RCTs comparing exon-skipping drugs with placebo in DMD. Trials were identified by searching published and unpublished studies from electronically available databases and clinical trial registries through October 2017. The primary outcomes were changes in the 6MWT distance, North Star Ambulatory Assessment (NSAA) scores, and AEs. Random-effects meta-analysis and assessment of risk of bias were performed. A total of 5 studies involving 322 participants were included, investigating eteplirsen in one and drisapersen in 4 studies. There were no changes in 6MWT distance (mean difference [MD] - 9.16, 95 % confidence interval [CI]: - 21.94 to 3.62) or NSAA scores (MD 1.20, 95 % CI: - 2.35 to 4.75) after 24 weeks of treatment in the exon-skipping group compared with placebo. Subgroup analysis for a 6 mg/kg weekly injection of drisapersen showed significant changes in the 6MWT, favoring drisapersen after 24 weeks (MD - 20.24; 95 % CI: - 39.59 to - 0.89). However, drisapersen resulted in a significant increase in injection site reactions (risk ratio [RR] 3.67, 95 % CI: 1.96 to 6.89, $p < 0.0001$) and renal toxicity (RR 1.81, 95 % CI: 1.11 to 2.94, $p = 0.02$). Risk of bias was high in 2 of the 5 studies, including the eteplirsen and 1 drisapersen study. The authors concluded that current available data do not show evidence that exon-skipping drugs are effective in DMD. Despite potential effectiveness when used at a specific dose, significant side effects were reported with drisapersen. The small number of RCTs with relatively small numbers of participants indicated the difficulty in conducting sufficiently powered studies of DMD. These researchers stated that prospectively planned meta-analysis and utilization of the real-world data may provide a more precise estimate of the effect of exon skipping in this disease.

Khan and co-workers (2019) noted that DMD patients experience skeletal muscle degeneration, including respiratory muscles. Respiratory decline in glucocorticoid-treated DMD patients, measured by percent predicted forced vital capacity (FVC% p), is typically 5 % annually in patients aged 10 to 18 years. These researchers examined the effects of eteplirsen on FVC% p annual change in 3 trials versus matched Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) controls. Eteplirsen studies 201/202 evaluated eligible ambulatory DMD patients for at least 4 years, study 204 evaluated primarily non-ambulatory DMD patients for 2 years, and ongoing study 301 is evaluating ambulatory DMD patients for 2 years (interim analysis was included). Eteplirsen-treated patients ($n=74$) were amenable to exon 51 skipping and were receiving glucocorticoids; 3 CINRG DNHS cohorts included: glucocorticoid-treated patients amenable to exon 51 skipping (Exon 51 CINRG DNHS; $n=20$), all glucocorticoid-treated CINRG patients (All CINRG DNHS; $n=172$), and all glucocorticoid-treated genotyped CINRG DNHS patients (Genotyped CINRG DNHS; $n=148$). FVC% p assessments between ages 10 and less than 18 years were included for all patients; mixed-model analyses characterized FVC% p annual change. FVC% p annual change was greater for CINRG DNHS Exon 51 controls (- 6.00) versus patients in studies 201/202, study 204, and study 301 (- 2.19, $p < 0.001$; - 3.66, $p < 0.004$; and - 3.79, $p < 0.017$, respectively). FVC% p annual change in all eteplirsen studies suggested treatment benefit compared with the Genotyped CINRG DNHS (- 5.67) and All CINRG DNHS (- 5.56) cohorts ($p < 0.05$, all comparisons). The authors concluded that significant, clinically meaningful attenuation of FVC% p decline was observed in eteplirsen-treated patients versus CINRG DNHS controls.

The authors stated that a potential limitation of this work was that a natural history study was used as a comparator rather than a randomized comparator. The differences between the clinical trial and natural history settings may have contributed to the observed disparities in pulmonary function decline. However, the 3 CINRG DNHS cohorts were selected using pre-specified criteria with respect to age range for pulmonary decline (10 to less than 18 years) and glucocorticoid treatment to match those of eteplirsen-treated patients, and they were contemporaneous cohorts. Further, the Exon 51 CINRG DNHS cohort and the eteplirsen-treated patients were matched for exon skipping-amenable mutations, making the natural history cohort an appropriate comparator. Comparisons of demographic and clinical characteristics between eteplirsen-treated patients and the CINRG DNHS cohort showed important differences. Eteplirsen-treated patients in studies 201/202 were younger and had higher FVC% p values than the CINRG DNHS cohort patients, while eteplirsen-treated patients in study 204 were older, with more advanced-stage disease. Interestingly, eteplirsen-treated patients from both studies showed slower decline in FVC% p than the CINRG DNHS cohort comparators.

The frequency and schedule of assessments were key protocol differences between the eteplirsen studies and the CINRG DNHS natural history study, which were addressed by the slope model analyses. However, the statistical models accounted for differences in variability between the eteplirsen studies and CINRG DNHS cohorts, and statistical significance was achieved in all cases despite these potential sources of variability. Another limitation of this work was that data from an interim analysis from 1 of the 3 eteplirsen trials (study 301) were used for the current analysis; further analysis at study completion is planned.

Alfano and colleagues (2019) described the outcomes of 2 non-ambulatory patients with DMD who participated in 2 clinical studies. The 2 consecutive trials of eteplirsen (studies 201 and 202) were conducted in patients with DMD (n=12) and confirmed genetic mutations amenable to exon 51 skipping. In study 201, a total of 12 patients were randomized to receive once-weekly, double-blind intravenous infusions of eteplirsen 30 or 50mg/kg or placebo for 24 weeks; patients then received open-label eteplirsen during weeks 25 through 28. All 12 patients continued onto open-label extension study 202 and received long-term treatment with eteplirsen. These researchers compared cardiac, pulmonary, and upper limb function and dystrophin production in the non-ambulatory twin patients versus the 10 ambulatory patients through 240 combined treatment weeks. A total of 10 study patients remained ambulatory through both studies, while the identical twin patients both experienced early, rapid loss of ambulation. The twin patients had greater disease severity at baseline (6MWT, 330 and 256m) versus the other patients (n=10; 6MWT range of 341 to 418m). They maintained cardiac and upper limb function through combined week 240, with outcomes similar to those of the patients who remained ambulatory. Dystrophin production was confirmed following eteplirsen treatment. The authors concluded that after loss of ambulation, disease progression was relatively stable in twin patients treated with eteplirsen and was similar to the mean of the study patients who remained ambulatory. The 2 patients who lost ambulation had the most progressed disease at initiation of treatment, experienced a rapid decline in ambulatory ability prior to confirmation of dystrophin production, and lost ambulation shortly thereafter. However, both patients experienced relative stability on non-ambulatory outcome measures. Each twin patient experienced maintenance of normal cardiac function and stability of upper limb function after losing ambulation. Sustained dystrophin expression was confirmed in both patients following 180 weeks of eteplirsen treatment by 3 complementary dystrophin assays. They stated that this observational study highlighted the potential benefit of eteplirsen in patients who are non-ambulatory or who lose ambulation during the course of treatment. As additional eteplirsen clinical trials progress, further evidence will become available to provide context for these clinical observations. The main drawbacks of this study included the observational nature of this analysis, the small number of patients (n = 2) evaluated, and the open-label nature of treatment in the extension study.

Hwang and Yokota (2019) noted that muscular dystrophy is a group of genetic disorders characterized by degeneration of muscles. Different forms of muscular dystrophy can show varying phenotypes with a wide range of age, severity and location of muscle deterioration. Many palliative care options are available for muscular dystrophy patients, but no curative treatment is available. Exon-skipping therapy aims to induce skipping of exons with disease-causing mutations and/or nearby exons to restore the reading frame, which results in an internally truncated, partially functional protein. In antisense-mediated exon-skipping synthetic antisense oligonucleotide binds to pre-mRNA to induce exon skipping. Recent advances in exon skipping have yielded promising results; the FDA approved eteplirsen (Exondys51) as the 1st exon-skipping drug for the treatment of DMD, and in-vivo exon skipping has been demonstrated in animal models of dysferlinopathy, limb-girdle muscular dystrophy type 2C and congenital muscular dystrophy type 1A. Novel methods that induce exon skipping utilizing Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are also being developed where splice site mutations are created within the genome to induce exon skipping. The authors concluded that challenges remain as exon-skipping agents can have deleterious non-specific effects and different in-frame deletions show phenotypic variance.

Golodirsen (Vyondys 53)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Vyondys 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Vyondys 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Golodirsen is available as Vyondys 53 (Sarepta Therapeutics, Inc.), which is an antisense oligonucleotide. Golodirsen is designed to bind to exon 53 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon 53 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping.

Vyondys 53 carries labeled warnings and precautions for hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation, and kidney toxicity, which was based on animal data. The most common adverse reactions (incidence 20% or more and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea (Sarepta, 2021b).

On December 12, 2019, the U.S. Food and Drug Administration (FDA) granted accelerated approved for Vyondys 53 (golodirsen) injection for the treatments of Duchenne Muscular Dystrophy (DMD) in patients with a confirmed mutation amenable to skipping exon 53. Golodirsen is designed to bind to exon 53 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Approval for this indication was based on results of a pivotal phase 1/2 clinical trial which found an increase in dystrophin production in skeletal muscle of patients treated with Vyondys 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials (Sarepta, 2019).

FDA approval was based on a two-part study. Study 1 Part 1, was a double-blind, placebo-controlled, dose-titration study in which male patients (median age of 8 years) were randomized to receive once-weekly intravenous infusions of golodirsen (n=8) in four increasing dose levels from 4 mg/kg to 30 mg/kg or placebo (n=4), for at least 2 weeks at each level. All patients who participated in Study 1 Part 1 (n=12) were continued into Study 1 Part 2, a 168-week, open-label study evaluating the efficacy and safety of golodirsen at a dose of 30 mg/kg IV once weekly. Part 2 included the 12 patients enrolled in Part 1, plus 13 additional treatment-naïve patients (total n=25) with DMD amenable to exon 53 skipping. Efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Part 2. Muscle biopsies were obtained at baseline prior to treatment and at Week 48 of Part 2 in all golodirsen-treated patients and were analyzed for dystrophin protein level by Western blot. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of Study 1 Part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels ($p < 0.001$); the median change from baseline was 0.88%. The most common adverse reactions (incidence $\geq 20\%$ and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea (Frank et al, 2020; Sarepta, 2021b).

Sarepta's placebo-controlled, post-marketing confirmatory trial (ESSENCE) to support the Vyondys 53 accelerated approval is currently enrolling and expected to conclude by 2024.

Viltolarsen (Viltepso)

U.S. Food and Drug Administration (FDA)-Approved Indications

- Viltepso is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping; this indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial (NS Pharma, 2021).

Viltolarsen is available as Viltepso (NS Pharma, Inc.), which is an antisense oligonucleotide. Viltepso is designed to bind to exon 53 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon 53 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping (NS Pharma, 2021).

Warnings and precautions for viltolarsen include kidney toxicity, which is based on animal data showing viltolarsen may cause kidney toxicity. Although kidney toxicity was not observed in the clinical studies with Viltepso, the clinical experience with Viltepso is limited, and kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients (NS Pharma, 2021).

The most common adverse reactions (incidence 15% or more) were upper respiratory tract infection, injection site reaction, cough, and pyrexia (NS Pharma, 2021).

Approximately 8% of patients with DMD have a mutation that is amenable to exon 53 skipping (FDA, 2020). Viltolarsen (Viltepso) is designed to bind to exon 53 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in

patients with genetic mutations that are amenable to exon 53 skipping (NS Pharma, 2021).

Viltolarsen (Viltepso) was evaluated in two clinical studies with a total of 32 patients, all of whom were male and had genetically confirmed DMD. The increase in dystrophin production was established in one of those two studies, a study that included 16 DMD patients, with 8 patients receiving Viltepso at the recommended dose. In the study, dystrophin levels increased, on average, from 0.6% of normal at baseline to 5.9% of normal at week 25 (FDA, 2020).

Study 1 (NCT0740972) was a multicenter, dose-finding, phase 2, 4-week randomized (double blind), placebo-controlled clinical trial for safety followed by a 20-week open-label treatment period conducted in the U.S. and Canada which evaluated the safety, tolerability, and efficacy of viltolarsen, a novel antisense oligonucleotide, in 16 ambulatory male participants (aged 4 to 9 years) with DMD amenable to exon 53 skipping. Primary outcomes of the trial included safety, tolerability, and de novo dystrophin protein production measured by Western blot in participants' biceps muscles. Secondary outcomes included additional assessments of dystrophin mRNA and protein production as well as clinical muscle strength and function. During the initial period (first 4 weeks) of Study 1, participants were randomized (double blind) to viltolarsen or placebo. All participants then received 20 weeks of open-label viltolarsen 40 mg/kg (n=8) or 80 mg/kg (n=8) once weekly. After 20 to 24 weeks of treatment, significant drug-induced dystrophin production was seen in both viltolarsen dose cohorts (40 mg/kg per week 5.7% of normal; 80 mg/kg per week 5.9% of normal). Viltolarsen was well tolerated; no treatment-emergent adverse events required dose reduction, interruption, or discontinuation of the study drug. No serious adverse events or deaths occurred during the study. Compared with 65 age-matched and treatment-matched natural history controls, all 16 participants treated with viltolarsen showed significant improvements in timed function tests from baseline, including time to stand from supine (viltolarsen: -0.19 s; control: 0.66 s), time to run/walk 10 m (viltolarsen: 0.23 m/s; control: -0.04 m/s), and 6-minute walk test (viltolarsen: 28.9 m; control: -65.3 m) at the week 25 visit. In conclusion, Study 1 found that in participants who received viltolarsen 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25. Thus, systemic treatment of participants with DMD with viltolarsen induced de novo dystrophin production, and clinical improvement of timed function tests was observed (Clemens et al., 2020; NS Pharma, 2021).

Inclusion criteria from Study 1 include the following:

- Males 4 years to less than 10 years of age;
- Confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin mRNA reading frame;
- Able to walk independently without assistive devices;
- Ability to complete the time to stand, time to run/walk 10 m and time to climb 4 stairs assessments; and
- Stable dose of glucocorticoid for at least 3 months.

In August 2020, the FDA granted accelerated approval to Viltepso (viltolarsen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. FDA approval was based on the data from Study 1 (NCT0740972) which demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 53 skipping. A clinical benefit of the drug has not been established. In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease, and the lack of available therapies. As part of the accelerated approval

process, the FDA is requiring the NS Pharma to conduct a clinical trial to confirm Viltepso's clinical benefit. The ongoing study is designed to assess whether Viltepso improves the time to stand for DMD patients with this confirmed mutation. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug (FDA, 2020).

Appendix

Appendix A - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 45 Skipping (not an all-inclusive list)

- Deletion of exon 44
- Deletion of exon 46-47
- Deletion of exon 46-48
- Deletion of exon 46-49
- Deletion of exon 46-51
- Deletion of exon 46-53
- Deletion of exon 46-55

Appendix B - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 51 Skipping (not an all-inclusive list)

- Deletion of exon 50
- Deletion of exon 52
- Deletion of exons 45-50
- Deletion of exons 47-50
- Deletion of exons 48-50
- Deletion of exons 49-50

Appendix C - Examples of DMD Gene Mutations (Exon Deletions) Amenable to Exon 53 Skipping (not an all-inclusive list)

- Deletion of exon 52
- Deletion of exon 45-52
- Deletion of exon 47-52
- Deletion of exon 48-52
- Deletion of exon 49-52
- Deletion of exon 50-52

References

The above policy is based on the following references:

1. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. Medicine (Baltimore). 2019;98(26):e15858.
2. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 2011;378(9791):595-605.
3. Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to Exon 53 skipping: A phase 2 randomized clinical trial. JAMA Neurol. 2020;77(8):1-10.
4. Darras BT. Treatment of Duchenne and Becker muscular dystrophy. UpToDate [online]

serial]. Waltham, MA: UpToDate; reviewed August 2016.

5. Fletcher S, et al. Dystrophin isoform induction in vivo by antisense-mediated alternative splicing. *The American Society of Gene & Cell Therapy*. 2010;18(6):1218-1223.
6. Frank DE, Schnell FJ, Akana C, et al, SKIP-NMD Study Group. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94(21):e2270-e2282.
7. Hwang J, Yokota T. Recent advancements in exon-skipping therapies using antisense oligonucleotides and genome editing for the treatment of various muscular dystrophies. *Expert Rev Mol Med*. 2019;21:e5.
8. Khan N, Eliopoulos H, Han L, et al; Eteplirsen Investigators and the CINRG DNHS Investigators. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2019;6(2):213-225.
9. Kole R, Krieg AM. Exon skipping therapy for Duchenne muscular dystrophy. *Adv Drug Deliv Rev*. 2015;87:104-107.
10. Mendell JR, Goemans N, Lowes LP, et al; Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016;79(2):257-271.
11. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-647.
12. Mendell JR, Sahenk Z, Lehman K, et al. Assessment of systemic delivery of rAAVrh74.MHCK7.micro-dystrophin in children with Duchenne muscular dystrophy: A nonrandomized controlled trial. *JAMA Neurol*. 2020;77(9):1122-1131.
13. Muntoni F, Murcuri E, McDonald C. ENVISION, a phase 3 randomized trial evaluating safety and efficacy of delandistrogene moxeparvovec (SRP- 9001) in Duchenne muscular dystrophy (DMD): Study design. Presented at the World Muscle Society, Charleston, USA; 3-7 October, 2023. P.47.
14. Muntoni F, Murcuri E, Schmidt UK, et al. EMBARK, a phase 3 trial evaluating safety and efficacy of delandistrogene moxeparvovec (SRP9001) in Duchenne muscular dystrophy (DMD): Study design and baseline characteristics (P5-8.012). *Neurology* Apr 2023, 100 (17 Supplement 2) 3691.
15. National Institutes of Health (NIH). Duchenne muscular dystrophy. Genetic and Rare Diseases Information Center (GARD). Bethesda, MD: NIH; updated May 7, 2020. Available at: <https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy>. Accessed August 18, 2020.
16. NS Pharma, Inc. Safety and dose finding study of NS-065/NCNP-01 in boys with Duchenne muscular dystrophy (DMD). ClinicalTrials.gov Identifier: NCT02740972. Bethesda, MD: National Library of Medicine; updated July 29, 2019.
17. NS Pharma, Inc. Viltepso (viltolarsen) injection, for intravenous use. Prescribing Information. Paramus, NJ: NS Pharma; revised March 2021.
18. Polavarapu K, Preethish-Kumar V, Sekar D, et al. Mutation pattern in 606 Duchenne muscular dystrophy children with a comparison between familial and non-familial forms: A study in an Indian large single-center cohort. *J Neurol*. 2019;266(9):2177-2185.
19. Randeree L, Eslick GD. Eteplirsen for paediatric patients with Duchenne muscular dystrophy: A pooled-analysis. *J Clin Neurosci*. 2018;49:1-6.
20. Sarepta Therapeutics, Inc. A gene transfer therapy study to evaluate the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in participants with Duchenne muscular dystrophy (DMD) (EMBARK). ClinicalTrials.gov ID: NCT05096221. Bethesda, MD: National Library of Medicine; updated November 7, 2023.
21. Sarepta Therapeutics, Inc. Amondys 45 (casimersen) injection, for intravenous use. Prescribing Information. Cambridge, MA: Sarepta Therapeutics; revised March 2023.
22. Sarepta Therapeutics, Inc. Elevidys (delandistrogene moxeparvovec-rokl) suspension, for intravenous infusion. Prescribing Information. Cambridge, MA: Sarepta Therapeutics; revised June 2024.
23. Sarepta Therapeutics, Inc. Exondys 51 (eteplirsen) injection, for intravenous use. Prescribing Information. Reference ID: 3987286. Cambridge, MA: Sarepta; revised

January 2022.

24. Sarepta Therapeutics, Inc. Sarepta Therapeutics announces FDA approval of Amondys 45 (casimersen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients amendable to skipping exon 45. Press Release. Cambridge, MA: Sarepta; February 25, 2021a.
25. Sarepta Therapeutics, Inc. Sarepta Therapeutics announces FDA approval of Elevidys, the first gene therapy to treat Duchenne muscular dystrophy. Press Release. Cambridge, MA: Sarepta Therapeutics; June 22, 2023c.
26. Sarepta Therapeutics, Inc. Sarepta Therapeutics announces FDA approval of Vyondys 53 (golodirsen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients amenable to skipping exon 53. Press Release. Cambridge, MA: Sarepta; December 12, 2019
27. Sarepta Therapeutics, Inc. Study of SRP-4045 and SRP-4053 in DMD patients (ESSENCE). ClinicalTrials.gov Identifier: NCT02500381. Bethesda, MD: National Library of Medicine; July 8, 2020.
28. Sarepta Therapeutics, Inc. Vyondys 53 (golodirsen) injection, for intravenous use. Prescribing Information. Cambridge, MA: Sarepta Therapeutics, revised February 2021b.
29. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: A systematic review and meta-analysis. *Orphanet J Rare Dis.* 2018;13(1):93.
30. U.S. Food and Drug Administration (FDA). FDA approves first gene therapy for treatment of certain patients with Duchenne muscular dystrophy. FDA News Release. Silver Spring, MD: FDA; June 22, 2023.
31. U.S. Food and Drug Administration (FDA). FDA approves targeted treatment for rare Duchenne muscular dystrophy mutation. FDA News Release. Silver Spring, MD: FDA; August 12, 2020.
32. U.S. Food and Drug Administration (FDA). FDA expands approval of gene therapy for patients with Duchenne muscular dystrophy. FDA News Release. Silver Spring, MD: FDA; June 20, 2024.
33. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. FDA News. Silver Spring, MD: FDA; September 19, 2016.
34. Vyondys 53™ (golodirsen) eDossier. AMCP Formulary Decisions. AmerisourceBergen Corporation. Conshohocken, PA. Available at: www.formularydecisions.com. Accessed April 15, 2020.
35. Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: An antisense oligonucleotide for potential treatment of exon 53 skipping in Duchenne muscular dystrophy. *Mol Ther Nucleic Acids.* 2018;13:442-449
36. Zaidman CM, Proud CM, McDonald CM, et al. Delandistrogene moxeparovovec gene therapy in ambulatory patients (aged ≥4 to <8 years) with Duchenne muscular dystrophy: 1-Year interim results from study SRP-9001-103 (ENDEAVOR). *Ann Neurol.* 2023;94(5):955-968.



coverage nor medical advice. This Clinical Policy Bulletin contains only a partial, general description of plan or program benefits and does not constitute a contract. Aetna does not provide health care services and, therefore, cannot guarantee any results or outcomes. Participating providers are independent contractors in private practice and are neither employees nor agents of Aetna or its affiliates. Treating providers are solely responsible for medical advice and treatment of members. This Clinical Policy Bulletin may be updated and therefore is subject to change.

Copyright © 2001-2025 Aetna Inc.

[Language services can be provided by calling the number on your member ID card. For additional language assistance:](#) [Español](#) | [Tiếng Việt](#) | [Tagalog](#) | [Русский](#) | [العربية](#) | [Kreyòl](#) | [Français](#) | [Polski](#) | [Português](#) | [Italiano](#) | [Deutsch](#) | [فارسی](#) | [Other Languages...](#) | [↗ \(http://www.aetna.com/individuals-families/contact-aetna/information-in-other-languages.html\)](http://www.aetna.com/individuals-families/contact-aetna/information-in-other-languages.html)