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Treatment for Duchenne Muscular Dystrophy

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as

safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

The use of antisense oligonucleotides (i.e., eteplirsen, golodirsen, viltolarsen, and casimersen) for the treatment of Duchenne muscular dystrophy **is considered not medically necessary** as a clinical benefit has not been established.

The use of antisense oligonucleotides (i.e., eteplirsen, golodirsen, viltolarsen, and casimersen) for the treatment of all other indications **is considered experimental, investigational and/or unproven**.

Policy Guidelines

None.

Description

Duchenne muscular dystrophy is an inherited disorder that results in progressive muscle weakness and loss of muscle mass, primarily affecting males. Duchenne muscular dystrophy results from non-sense or frame-shifting variant(s) in the *Duchenne muscular dystrophy* gene which is responsible for producing dystrophin, a cohesive protein essential for maintaining muscle support and strength. Antisense oligonucleotides are short, synthetic, single-stranded oligodeoxynucleotides that selectively bind to specific exons of the dystrophin pre-messenger RNA causing the exon to be skipped and thereby repairing the mutated reading frame resulting in production of an internally truncated, yet functional, dystrophin protein. Four antisense oligonucleotides—eteplirsen, golodirsen, viltolarsen, and casimersen have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of Duchenne muscular dystrophy. Each targets a specific exon. For example, eteplirsen targets skipping of exon 51, golodirsen and viltolarsen target skipping of exon 53, and casimersen targets skipping of exon 45.

Background

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 males. (5) Although it primarily affects males, a small number of females are also affected but are usually asymptomatic. Even when symptomatic, most females typically only present with a mild form of the disease. According to U.S. epidemiologic data, the first signs or symptoms of Duchenne muscular dystrophy are noted at a mean age of 2.5 years (range, 0.2 to 1 year), and the mean age at definitive diagnosis is 4.9 years (range, 0.3 to 8.8 years). (6) Symptoms include motor difficulties such as difficulty running, jumping, and walking up stairs, along with an unusual waddling gait. Some improvement in symptoms may be seen from 3 to 6 years of age, though gradual deterioration resumes, and most patients lose ambulation by age 12 and require noninvasive ventilation by the late teenage years. Patients progress from needing noninvasive ventilation only during night sleeping, followed by noninvasive ventilation during day and night sleeping, and then noninvasive ventilation during day and night over the course of 5 to 10 years.

Duchenne muscular dystrophy occurs as a result of variant(s) in the gene responsible for producing dystrophin, a cohesive protein that is essential for maintaining muscle support and strength. *Duchenne muscular dystrophy* is the longest known human gene, and several variants can cause Duchenne muscular dystrophy. Most deletion variants disrupt the translational reading frame in the dystrophin messenger RNA resulting in an unstable, nonfunctional dystrophin molecule. As a result, there is progressive muscle degeneration leading to loss of independent ambulation, as well as other complications, including respiratory and cardiac complications. (7) Genetic testing is required to determine the specific *Duchenne muscular dystrophy* gene variant(s) for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 variants in the Leiden Duchenne muscular dystrophy mutation database, and the most common variants are concentrated between exons 45 and 53.

Regulatory Status

Eteplirsen

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) for treatment of Duchenne muscular dystrophy patients who have a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some participants treated with eteplirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a confirmatory trial to demonstrate the clinical benefit of eteplirsen. In the years after the FDA approval, there has still been no publication of a trial confirming or refuting a clinical benefit of eteplirsen. The European Medicines Agency rejected marketing approval for eteplirsen in September 2018. (8)

Golodirsen

In December 2019, golodirsen (Vyondys 53™; Sarepta Therapeutics) was approved by the FDA for treatment of Duchenne muscular dystrophy patients who have a confirmed variant of

the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some participants treated with golodirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a randomized, double-blind, placebo-controlled trial of 96 weeks with an open-label extension to 144 weeks to verify the clinical benefit of golodirsen with the primary endpoint of a 6-minute walk test.

Viltolarsen

In August 2020, viltolarsen (Viltepso™; Nippon Shinyaku Co.) was approved by the FDA for the treatment of Duchenne muscular dystrophy patients who have a confirmed mutation of the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in participants treated with viltolarsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Nippon Shinyaku Co. conduct a randomized, double-blind, placebo-controlled trial over 48 weeks to verify the clinical benefit of viltolarsen with the primary endpoint "time to stand".

Casimersen

In February 2021, casimersen (Amondys 45™; Sarepta Therapeutics) was approved by the FDA for the treatment of Duchenne muscular dystrophy patients who have a confirmed mutation of the *Duchenne muscular dystrophy* gene that is amenable to exon 45 skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in participants treated with casimersen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta verify the clinical benefit of casimersen by completing Study 4045-301 (Essence), A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in participants with Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96 weeks and concludes after an open label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or

worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Antisense Oliogonucleotides for Treatment of Duchenne Muscular Dystrophy

Clinical Context and Therapy Purpose

The purpose of antisense nucleotides such as eteplirsen, golodirsen, viltolarsen, and casimersen in individuals who have a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping.

Interventions

The therapies being considered are antisense oligonucleotides such as eteplirsen, golodirsen, viltolarsen, and casimersen. Phosphorodiamidate morpholino oligomers are stable oligonucleotide analogues that selectively bind to RNA to alter gene expression. In the case of eteplirsen, the phosphorodiamidate morpholino oligomer binds to exon 51 of the dystrophin pre-messenger RNA causing the exon to be skipped and prevents that part of the code from being read during messenger RNA processing, thereby partially repairing the mutated reading frame in the messenger RNA coding sequence. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein. Similarly, golodirsen and viltolarsen target skipping of exon 53 and casimersen targets skipping of exon 45.

Comparators

There is no cure for Duchenne muscular dystrophy (DMD). Treatment is aimed at controlling symptoms to improve quality of life.

The following practice is currently being used to treat patients with a confirmed variant of the *Duchenne muscular dystrophy* gene: standard multidisciplinary care including pharmacotherapy. Pharmacotherapy primarily involves corticosteroids (mainly prednisone or deflazacort) for all individuals regardless of the genetic variant. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but before the onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications. In addition, muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed. (5)

Outcomes

The general outcomes of interest are a change in disease status, functional outcomes, quality of life, treatment-related mortality, and treatment-related morbidity. See Table 1 for the description and relevance of specific outcome measures considered in this policy.

As per the U.S. Food and Drug Administration (FDA) guidance document for developing drugs for the treatment of dystrophinopathies, the FDA has no defined set of required or recommended clinical outcome measures to be used in clinical studies. The guidance states that manufacturers should propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Further, it states, "The sponsor should include an assessment of multiple efficacy endpoints, when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the primary endpoint is only 1 of these measures." (9)

Table 1. Health Outcome Measures That May Be Relevant to Muscular Dystrophinopathies

Outcome Measure	Description	Scale	Clinically Meaningful Difference/Comment
Griffiths scale of mental development	Comprehensive, child friendly developmental measure for continuous use from birth to 6 years (72 months).	Consists of 2 sets of scales, 1 for each age group 0-2 years and 2-8 years.	Although used in Duchenne muscular dystrophy, this is a non-specific measure and its appropriateness to measure clinical efficacy for Duchenne muscular dystrophy has not been established.
Bayley scales of infant and toddler development (Third edition)	Designed to assess developmental functioning from 1 month to 42 months of age. Covers 5 domains: cognitive,	Composite scores are derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100,	Although used in Duchenne muscular dystrophy, this is a non-specific measure and its appropriateness to

	language, motor, adaptive, and social emotional development.	standard deviation of 15, and range of 40 to 160.	measure clinical efficacy for Duchenne muscular dystrophy has not been established.
NSAA or an age appropriate modified NSAA	Measures functional motor abilities. Appropriate for ambulatory children ages ≥3 years of age with Duchenne muscular dystrophy.	17-item scale that grades each activity from 0 (unable to achieve independently) to 2 (normal- no obvious modification of activity). Scores can range from 0 to 34. Higher scores indicate improvement. Also includes recording timed items such as the 10-meter timed walk/run test and time to rise from the floor (Gower's test). These times are not included in the global score.	Not reported
6MWT or shorter versions such as the 2-minute walk test	Measures strength and endurance and can be appropriate for patients as young as 5-6 years of age. Performance may increase with time in very young patients whereas performance tends to worsen with time in older patients. Floor effect of losing ambulation in older patients with more advanced disease and analyses of change in 6MWT can be strongly influenced by the inclusion or exclusion of patients who lose ambulation	Assesses distance walked in 6 minutes.	Estimates of minimum clinically important difference for Duchenne muscular dystrophy patients of a change of 30 meters have been reported. (10, 11) Interpretation of 6MWT results is limited by the variability in testing procedures and patient motivation.

	during the trial; such patients contribute zero values.		
Myometric assessments	Appropriate to measure increase or preserv muscle strength, and it can be used to provide reliable measurements in children ages 5 years and older.		Clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Specific clinical respiratory outcomes	Nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation.	Varied outcome measure (dichotomous or continuous).	Clinical meaningfulness of differences should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Biomarker (such as dystrophin)	Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker and as a potential surrogate endpoint for accelerated approval.	Dystrophin levels are measured in muscle fibers by immunohistochemical analysis to detect the presence or absence of dystrophin regardless of the actual quantity of dystrophin present while Western blot analysis quantifies the amount of dystrophin in the muscle tissue sample.	Dystrophin expression can only be viewed as supportive of the proof of principle. It is currently uncertain how predictive of sustained functional improvement the detected dystrophin level could be, and what levels may be required for a meaningful clinical improvement in Duchenne patients to be registered. Further, dystrophin produced by eteplirsen is an internally shortened protein and the clinical effect of the truncated

			dystrophin is still not fully known.

6MWT: 6-minute walk test; NSAA: North Star Ambulatory Assessment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Eteplirsen

The clinical development program of eteplirsen is summarized in Table 2. In addition, exploratory post-hoc analysis from these studies have also been published.

Table 2. Summary of the Clinical Development Program for Eteplirsen

Trial	NCT	Phase	Description	N	Design	Status
STUDY 201/202	NCT01396239	2	Treatment of ambulant subjects with Duchenne muscular dystrophy	12	DBRCT	Completed and published (12)
STUDY 204	NCT01540409	2	Rollover Study of Study 204 with a follow-up of 4 years	12	Open-label	Completed and published (13)
STUDY 301	NCT02255552 (PROMOVI)	3	Treatment of ambulant subjects aged 7 to 16 years with Duchenne muscular dystrophy	109	Open-label with concurrent untreated control arm	Completed and published (14)

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial; NCT01396239: A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability and Pharmacokinetics Study of AVI-4658 (Eteplirsen), in the Treatment of Ambulant Subjects With Duchenne Muscular Dystrophy and Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects With Duchenne Muscular Dystrophy Who Participated in Study 4658-US-201; NCT01540409: Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects With Duchenne Muscular Dystrophy Who Participated in Study 4658-US-201; NCT02255552: An Open-Label,

Multi-Center, Study With a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy.

Randomized Controlled Trials

Study 201 is single-center, double-blind, placebo-controlled trial that randomized 12 males ages 7 to 13 years with DMD amenable to exon 51 skipping and on stable corticosteroid dose for at least 6 months to eteplirsen (30 or 50 mg/kg/week) or placebo (4 participants per group) (Table 3). Treatment continued for 24 weeks and then placebo participants switched to eteplirsen 30 or 50 mg/kg (n=2 per group) at week 25. The primary trial endpoint was a measure of the change in dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry. (15) The results published in 2013 reported a substantial increase (range, 23%-52%) in the percentage of dystrophin-containing fibers in the biopsy specimens at weeks 24 and 48 in the eteplirsen-treated groups. (12) However, immunohistochemistry analysis is not a quantitative measure of dystrophin. This analysis evaluates thin slices of muscle biopsies to assess whether dystrophin is present or absent. Each muscle fiber showing any amount of dystrophin counts as positive, regardless of the actual quantity of dystrophin present. On the other hand, Western blot analyzes how much dystrophin is present in a sample. Results reported in the prescribing label showed that the average dystrophin protein level after 180 weeks of treatment with eteplirsen measured by Western blot analysis of biopsy was 0.93% of the dystrophin level in healthy subjects. A more rigorous and fully blinded reanalysis of the FDA immunohistochemical assay by 3 investigators cast further doubt about the consistency of immunohistochemical analysis because there was little difference in positive fibers between original baseline samples and week 180. (16)

Observational Studies

Study 202 was a 4-year open-label trial that enrolled all participants from Study 201. The trial was designed to assess the ongoing efficacy and safety of eteplirsen. Individuals continued on the same dose of eteplirsen they received at the end of Study 201 (6 participants on 30 mg/kg and 6 participants on 50 mg/kg (Table 3). The prespecified clinical endpoints for the 6-minute walk test for study 201 (week 24) and study 202 (week 48) were negative. (16) The article reported a 67.3-meter benefit in the 6-minute walk test distance at week 48 in ambulation-evaluable eteplirsen-treated participants (n=6) compared with placebo/delayed participants ($p<.005$). (12) However, this was a post-hoc analysis excluding 2 eteplirsen-treated participants who quickly deteriorated while receiving therapy and lost ambulation beginning at week 4 of the trial. The FDA has recommended retraction of the published study due to concerns about the interpretation of its findings. (17) Further, in an exploratory analysis, the FDA found no correlation between dystrophin levels and the 6-minute walk test distance. (16) For example, among the 4 participants with the most preserved 6-minute walk test, 2 had the lowest and 2 had the highest dystrophin levels as determined by Western blot. As per the prescribing label, there was no significant difference in change in 6-minute walk test distance between participants treated with eteplirsen and placebo. The use of the 6-minute walk test as an objective outcome instrument is limited by factors such as influence due to expectation bias, motivation, and coaching. Participants in the pivotal 201/202 trial were aware of treatment assignment for most of the investigation period.

McDonald et al. (2021) reported the results of the PROMOVI, an open-label study which enrolled 79 ambulatory participants aged 7 to 16 years with confirmed mutations amenable to exon 51 skipping. (14) These participants received the FDA approved dose of 30 mg/kg/week eteplirsen intravenously for 96 weeks. An untreated cohort with DMD not amenable to exon 51 skipping was also enrolled to serve as a control arm. Of the 79 participants enrolled in the eteplirsen cohort, 78 completed 96 weeks of treatment. In the untreated control arm, 15 of the 30 enrolled untreated participants completed the study. Post-hoc, authors deemed this control arm to be an inappropriate control group citing genotype-driven differences in clinical trajectory. Instead, the authors utilized post-hoc comparisons with participants from eteplirsen pivotal studies 201/202 and mutation-matched external natural history controls. Reported results showed attenuation of decline on the 6-minute walk test over 96 weeks (PROMOVI: -68.9 m; phase 2 studies [201/202] of eteplirsen: -67.3 m; external controls: -133.8 meters) and significant attenuation of percent predicted forced vital capacity annual decline (PROMOVI: -3.3%, phase 2 studies: -2.2%, external controls: -6.0%; p <.001). A comparison of clinical outcomes of eteplirsen-treated cohort with untreated cohort with DMD not amenable to exon 51 skipping was not reported.

Additional analysis reporting long-term data from studies 201/202 with multiple cutoffs dates reporting multiple clinical outcomes and their comparison with historical control has been published. These are summarized below. Interpretation of these results is confounded by unobserved or unadjusted baseline differences in prognostic variables between the groups.

Eteplirsen's manufacturer reported to the FDA Peripheral and Central Nervous System Drugs Advisory Committee meeting a gain of 162 meters on the 6-minute walk test at 4 years after treatment with eteplirsen in 12 participants in study 202 compared with 13 participants from an external control. (15) Results were subsequently published by Mendell et al. (2016) (13) in a peer-reviewed journal. Data for external controls were extracted from pooled data from an Italian and Belgian registry by matching corticosteroid use at baseline, availability of longitudinal data for the 6-minute walk test, age, and genotype amenable to exon 51 skipping therapy. However, the FDA (15) and others (18) have identified several issues related to the use of an external control such as differences in the use of steroids and physical therapy between the 2 groups. Most importantly, the impact of unknown prognostic factors cannot be ascertained in an externally controlled study.

Published studies suggest a linear annual decline of approximately 5% in the percent predicted forced vital capacity (FVC%) in participants with Duchenne muscular dystrophy, regardless of corticosteroid treatment. (19) Khan et al. (2019) summarized the mean annual decline in FVC% of eteplirsen-treated participants from studies 202 and 204, as well as interim results from 42 participants in study 304, and compared the results with a matched control group of glucocorticoid-treated Duchenne muscular dystrophy individuals aged 10 to <18 years drawn from a registry with mutations amenable to exon 51 skipping (n=20). (20) Data on matched controls were obtained from prospective natural history studies of more than 400 Duchenne muscular dystrophy participants. (21) The data are summarized in Table 6. Compared to the

matched control group, eteplirsen-treated participants had a statistically significant slower decline in the annual rate of FVC%. Use of historical controls is problematic as the results are prone to bias, particularly if there is disease heterogeneity or change in diagnostic abilities or treatment standards over time. The above outcomes require careful evaluation and may not be appropriate evidence for evaluating a therapy even for an ultra-rare condition.

Kinane et al. (2018) reported long-term data (240 weeks or approximately 4.6 years) on pulmonary function outcomes of 12 participants from the pivotal study 201/202. (22) Results were compared with a historical natural cohort consisting of 34 participants who participated in the United Dystrophinopathy Project aged 7 to 15.5 years who had undergone pulmonary function testing. The annual decrease in FVC% in the eteplirsen and historical cohort was 2.3% (95% confidence interval [CI], 1.2% to 3.4%) and 4.1% (95% CI, 1.9% to 6.3%) respectively. Alfano et al. (2019) reported outcomes from the original cohort of 12 participants from the pivotal study 201/202. (23) It is unclear if the results of these studies provide any incremental information from the previously published studies that could meaningfully alter conclusions about the net health benefit of eteplirsen in participants with Duchenne muscular dystrophy amenable to exon 51 skipping.

Mitelman et al. (2022) reported analysis of 12 participants from study 201/202 with a median follow-up of approximately 6 years of eteplirsen treatment. (24) Outcomes included loss of ambulation and FVC%. Outcomes were compared between eteplirsen-treated participants and historical external controls. Compared to historical controls, eteplirsen-treated participants experienced a statistically significant longer median time to loss of ambulation by 2.09 years (5.09 vs. 3.00 years, p <.01) and significantly attenuated rates of pulmonary decline versus historical control (FVC % change: -3.3 vs. -6.0 percentage points annually, p<.0001).

Iff et al. (2023) reported results of a retrospective analysis of real-world claims and electronic medical record data comparing 389 individuals with DMD who received eteplirsen to 389 matched controls. (25) The data were from the Clarivate Real-World Data repository which includes more than 300 million patients and claims to be representative of the population of all US states. Data from January 2011 to June 2021 were included. Individuals were included if they were less than 40 years of age at the first observed diagnosis for DMD or the initiation of eteplirsen treatment, had a pre-index period of observation of 12 months, and a follow-up period of at least 6 months. For eteplirsen-treated individuals, the index date was the earliest observed date with an eteplirsen prescription or injection. For the control group, the index date was the time at which the matched eteplirsen-treated patient-initiated treatment. A two-step matching approach was used: 1) each treated patient was matched exactly to control patients with the same age and health stage at the index date; 2) propensity score matching was used to select the most comparable control based on the rates of the main DMD-related healthcare resource utilization procedures and events within the pre-index period. The design and analysis were reportedly pre-specified. At index date, the mean (SD) age was 13 [6] years, 20% were in the early ambulatory stage, 17% were in the late ambulatory stage, 43% were in the early non-ambulatory stage, and 19% were in the late non-ambulatory stage. About 32% of individuals had exposure to steroid treatment prior to eteplirsen treatment. The mean (standard deviation

[SD]) duration of eteplirsen treatment was 29 [20] months. The mean (SD) follow-up duration was of 37 [16] months. Eteplirsen treatment was associated with statistically significant reductions in rates of hospital encounters (31%), emergency room visits (31%), need for pulmonary management (33%), cardiac management (21%), tracheostomy (86%), and assisted ventilation (39%) versus the control group. For several other outcomes (cough assist device, intensive care unit [ICU] days, motorized wheelchair, and scoliosis), the results numerically favored eteplirsen but were not statistically significantly improved.

Safety

The majority of adverse events observed in the clinical trials of eteplirsen were considered to be mild or moderate. Overall, 8 severe adverse events (incision site hemorrhage, hemorrhoids, back pain, cardiomyopathy, nasal congestion, balance disorder, bone pain, and femur fracture) were observed during the clinical trial program of eteplirsen. Except for the cardiomyopathy, which occurred during a dose-ranging trial of eteplirsen, all were considered not to be related to the use of eteplirsen. (15)

Table 3. Summary of Key Study Characteristics

Study; Trial	**Country**	**Design**	**Sites**	**Duration**	**Participants**	**Interventions**	
						Active	Comparator
Study 201							
Mendell et al. (2013) (12)	U.S.	RCT	1	24 weeks	Patients with Duchenne muscular dystrophy ages 7-13 years with confirmed deletions amenable to skipping exon 51 and ability to walk 200-400 m on 6MWT and on glucocorticoids for ≥24 weeks.	eteplirsen 30mg/kg/ week (n=4); eteplirsen 50 mg/kg/week (n=4)	Placebo (n=4)
Study 202							
Mendell et al. (2016) (13)	U.S.	Open label	1	4 years	All patients from study 201 were enrolled in study 202.	eteplirsen 30 mg/kg/week (n=6); eteplirsen 50 mg/kg/week (n=6)	None

Study 301							
Khan et al. (2019) (20)	U.S.	Open label, ongoing study[a]	37	96 weeks	Patients with Duchenne muscular dystrophy ages 7-16 years with confirmed deletions amenable to skipping exon 51 and ability to walk >300 m on 6MWT and on glucocorticoids for ≥24 weeks.	Eteplirsen 30 mg/kg/week (n=12); target is 80 participants	Untreated controls of patients with Duchenne muscular dystrophy not amenable to exon 51 skipping

RCT: randomized controlled trial; 6MWT: 6-minute walk test; U.S.: United States; yrs: years;
[a] This study was ongoing at the time of publication of this paper (PROMOVI; NCT02255552). The FDA asked Sarepta for additional data for review and Sarepta provided information on 13 individuals currently enrolled in the PROMOVI trial who had baseline and 48-week data.

Table 4. Summary of Pivotal Trial Results

Study	**Mean Percent Change in Dystrophin Level From Baseline (SE)**			**Mean Change in 6MWT (SE), Meters**	
	Study 201		Study 202	Study 201	Study 202
	Week 12	Week 24	Week 48	Week 24	Week 48
Mendell et al. (2013) (12)					
All eteplirsen (n=8)	NR	NR	47.3 (3.9)[a]	NR	NR
30-mg (n=4)	NR	22.9 (2.9)[a]	51.7 (3.5)[a]	14.2 (14.4)[b]	31.5 (19.9)[b, c]
50-mg (n=4)	0.8 (3.5)	NR	42.9 (6.7)[a]	-0.3 (31.2)	21.0 (38.2)[c]
Placebo (n=4)	-4.0 (2.9)	-4.0 (2.9)	37.7 (6.3)[a]	-25.8 (30.6)	-68.4 (37.6)
30-mg delayed (n=2)	NR	-7.5 (1.0)	33.6 (5.2)	NR	NR
50-mg delayed (n=2)	-0.6 (5.2)	NR	41.8 (13.3)	NR	NR
	Mean Percent Normal Dystrophin (SD)				
	Study 301 Baseline		Study 301 Week 48	Study 301 p	
Exondys Prescribing Label (2024) (1)	0.16		0.44	0.008	

6MWT: 6-minute walk test; mg: milligram; NR: not reported; SD: standard deviation; SE: standard error;

[a] p<0.01 vs. baseline
[b] Excluding 2 individuals who showed rapid disease progression at week 4 of study.
[c] p<0.001 vs. delayed eteplirsen group.

Table 5. Summary of Pivotal Trial Results (Functional Outcomes) Compared to Historical Controls

	6MWT, mean meters (SD)					Loss of Ambulation, n (%)				
	Baseline	Year 1	Year 2	Year 3	Year 4	Baseline	Year 1	Year 2	Year 3	Year 4
Mendell et al. (2016) (13)										
Eteplirsen (n=12)	363.2 (42.2)	305.8 (155.3)	295.9 (149.0)	263.1 (151.7)	196.3 (130.2)	All ambulatory	2 (17)	2 (17)	2 (17)	2 (17)
External control (n=13)[a]	257.6 (66.8)	318.6 (94.2)	223.5 (145.4)	110.3 (136.2)	27.3 (90.3)	-	All ambulatory	3 (23)	6 (46)	10 (77)

Adapted from The Institute for Clinical and Economic Review Evidence Report.
6MWT: 6-minute Walk Test; SD: standard deviation.
[a] Two historical control patients did not have data at all time points; 1 contributed until year 1, and the second contributed until year 2.

Table 6. Summary of Key Study Results (Pulmonary Outcomes) Using Historical Controls

Matched Control/Trials (21)	Number of observations	Baseline Mean	Mean Annual Change (SE) in FVC%	Difference in Annual Change Versus Control, 95% CI	P-value
Matched Control (n=20)	88	79.6 (13.3)	-6.00 (0.41)	Reference	-
Study 201/202 (n=12)	132	96.9 (14.0)	-2.19 (0.71)	3.81 (2.19 to 5.42)	<0.001
Study 204 (n=20)	117	65.9 (16.6)	-3.66 (0.68)	2.34 (0.77 to 3.90)	0.004
Study 301 (n=42)	184	78.5 (15.7)	-3.79 (0.82)	2.21	0.017

Adapted from The Institute for Clinical and Economic Review Evidence Report.
CI: confidence interval; FVC%: percent predicted forced vital capacity; n: number; SE: standard error.

The purpose of limitations tables (Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following

each table and provides conclusions on the sufficiency of the evidence supporting the position statement.

Table 7. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Mendell et al. (2013) (12) Study 201				2. Primary endpoint was physiologic measure (dystrophin level) and correlation with clinical benefit is unknown. 4. Dystrophin measured by IHC staining which only reports presence or absence, verses Western blot which measures quantity of dystrophin. 6. Clinically significant difference not supported.	
Mendell et al. (2016) (13) Study 202				5. Clinically significant difference for 6MWT was not pre-specified. 6. Clinically significant difference not supported.	
Khan et al. (2019) (20) Study 301				5. Clinically significant difference for percent predicted forced vital capacity was not pre-specified. 6. Clinically significant difference not supported.	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

6MWT: 6-minute Walk Test; IHC: immunohistochemical;

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mendell et al. (2013) (12) Study 201	3. No description of randomization procedure or subsequent concealment	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		5. Inappropriate exclusions (2 of 8 patients in treatment arms who lost ambulation were excluded from 6MWT analysis)	1.Small sample size (each arm had 4 participants)	
Mendell et al. (2016) (13) Study 202	1. Participants not randomly allocated 4. Inadequate control for selection bias.	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician			1.Small sample size (arms had 2 or 4 participants)	
Khan et al. (2019) (20) Study 301	1. Participants not randomly allocated 4. Inadequate control for selection bias.	1. Not blinded to treatment assignment 2. Not blinded outcome assessment		1. High loss to follow-up or missing data (preliminary results of an ongoing study-results from		

		3. Outcome assessed by treating physician		42 of an expected 109 participants)		

The study limitations stated in this table are those notable in the current policy; this is not a comprehensive gaps assessment. 6MWT: 6-minute Walk Test;

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important differences.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Eteplirsen for Treatment of Duchenne Muscular Dystrophy

Evidence for the use of eteplirsen for the treatment of Duchenne muscular dystrophy amenable to exon 51 skipping includes a single RCT and an ongoing, prospective, open-label trial with a concurrent untreated control arm. In addition, multiple post-hoc studies with longer follow-up and use of historical comparators have also been published. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total participants was selected with 4 participants in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in 6-minute walk test distance or change in North Star Ambulatory Assessment total score between eteplirsen-treated participants and placebo-treated participants at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analyses of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen-treated participants was less as compared to historical controls. However, the post-hoc nature of the analysis and the fact that the cohorts were retrospectively identified within the untreated group of participants is of serious concern

due to potential selection bias and undermines the robustness of the data. Particularly, the 6-minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus, the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping.

Golodirsen

The clinical development program of golodirsen for individuals with Duchenne muscular dystrophy includes a 2-part multicenter study, which is summarized in Table 9.

Table 9. Summary of the Clinical Development Program for Golodirsen

Trial	NCT	Phase	Description	N	Design	Status
SKIP-NMD (2, 17, 26)	NCT02310906	1/2	Dose-finding (part 1) and efficacy and safety (part 2)	39	DBRCT (part 1) and open-label (part 2)	Complete and unpublished

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial; SKIP-NMD: Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in PATIENTS With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping.

Pivotal Trial

Trial characteristics and results of the pivotal SKIP-NMD trial are summarized in Tables 10 and 11, respectively. This trial consisted of 2 parts: part 1 of the trial was for 12 weeks with the primary intent to assess safety and tolerability while the primary intent of part 2 was to assess change from baseline in 6-minute walk test at 144 weeks and change in dystrophin protein levels at 48 weeks. Results are summarized in Table 11. (2, 26) Results included a pre-planned interim analysis of dystrophin levels, dystrophin intensity, and exon-skipping from paired muscle biopsies of the biceps brachii from 25 participants receiving weekly intravenous infusions of golodirsen 30 mg/kg at baseline and week 48. Biopsies were examined using a Western blot method to quantify dystrophin production (primary biological endpoint). Exon 53 skipping was evaluated using reverse transcription-polymerase chain reaction. An automated image analysis (MuscleMap™) used immunohistochemistry to assess dystrophin localization and sarcolemma fiber intensity.

Table 10. Summary of Trial Characteristics of a Key Randomized Trial of Golodirsen

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
SKIP-NMD (2, 26, 27)	U.S., France,	5	2015-2019	• Males aged 6 to 15 yrs (N=25)	Part 1 (12 weeks):	Part 1 (12 weeks):

	Italy, and U.K.			• Diagnosed with DMD, confirmed by a genetic test • Stable cardiac and pulmonary function • Stable dose of corticosteroids for at least 6 m • Major exclusions[a] • Two-part study[b,c]	Golodirsen escalating dose (n = 8) Part 2 (up to 168 weeks): (n = 25)	Placebo (n=4) Part 2 (up to 168 weeks): Untreated group not amenable to exon 53 skipping (n=24)

DMD: Duchenne muscular dystrophy; n: number; SKIP-NMD: Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in patients With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping; U.K.: United Kingdom; U.S.: United States.

[a] Previous treatment with the experimental agents BMN-195 (SMT C1100) or PRO053; current or previous treatment with any other experimental treatments within 12 weeks prior to study entry; major surgery within the last 3 months; presence of other clinically significant illness; major change in physical therapy regimen within the last 3 months.

[b] Part 1, primarily assessed safety and tolerability.

[c] Part 2, the primary endpoints were change from baseline in 6MWT at 144 weeks and change in dystrophin protein levels at 48 weeks. Secondary endpoints included drug pharmacokinetics, change from baseline in FVC percent predicted, and change from baseline in dystrophin intensity at 144 weeks.

Table 11. Summary of Efficacy Results of a Key Randomized Trial of Golodirsen

Study	% Change in mean normal dystrophin protein	6MWT	Pulmonary Function	Safety
SKIP-NMD (6, 26, 27)				
N	25	NR	NR	41
Golodirsen	Baseline: 0.095% Week 48: 1.019% Change: +0.924%[a]	NR	NR	The most common adverse reactions (incidence ≥20% and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.
Untreated group (non-exon 53)	NR	NR	NR	NR
Diff (95% CI)	Cannot be assessed	Cannot be assessed	Cannot be assessed	-

p-value	Cannot be assessed	Cannot be assessed	Cannot be assessed	-

[a] As per The Institute for Clinical and Economic Review Report, the absolute increase in mean dystrophin levels was from 0.918% to just over 1% of normal in patients treated for 48 weeks.
6MWT: 6-minute walk test; CI: confidence interval; Diff: difference; N: number; NR: not reported; SKIP-NMD: Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping.

The purpose of limitations tables (Tables 12 and 13) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 12. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
SKIP-NMD (2, 17, 26)				2. Primary endpoint was a physiologic measure (dystrophin level) and correlation with clinical benefit is unknown. 6. Clinically significant difference not supported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
SKIP-NMD: Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]

SKIP-NMD (2, 17, 26)	3. No description of randomization procedure or subsequent concealment.				1. Power calculations not reported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
SKIP-NMD: Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Golodirsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping who receive golodirsen, the evidence includes a 2-part multicenter study, which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Results of an interim analysis were based on 25 participants who received a weekly intravenous infusion of golodirsen 30 mg/kg. At week 48, the mean change in dystrophin protein levels was a 0.924% increase from the baseline (1.019% vs. 0.095%; p<.001). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with golodirsen will translate into a clinical benefit to patients. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of golodirsen in patients with Duchenne muscular dystrophy amenable to 53 skipping.

Viltolarsen

The clinical development program of viltolarsen for individuals with Duchenne muscular dystrophy includes a single 2-period, dose-finding study conducted in the United States and Canada summarized in Table 14.

Table 14. Summary of the Clinical Development Program for Viltolarsen

Trial	NCT	Phase	Description	N	Design	Status
NS-065/ NCNP-01-201	NCT02740972	2	4-week randomized for safety followed by a 20-week open-label treatment period of participants aged 4 to 9 years with DMD	16	DBRCT (part 1) and open-label (part 2)	Complete and published (28)

DBRCT: double-blind randomized controlled trial; DMD: Duchenne muscular dystrophy; NCT: national clinical trial.

Pivotal Trial

Trial characteristics and results of the pivotal trial are summarized in Tables 15 and 16, respectively. This trial consisted of 2 parts: part 1 of the trial was of 4 weeks duration with the primary objective of safety and tolerability; part 2 had a primary objective of evaluation of the change in dystrophin protein levels at week 25. As reported in the prescribing label, in participants who received viltolarsen 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (±0.8) of normal at baseline to 5.9% (±4.5) of normal by week 25 with a mean change in dystrophin of 5.3% (±4.5) of normal levels (p=.01) as assessed by validated Western blot (normalized to myosin heavy chain).The median change from baseline was 3.8%. All participants demonstrated an increase in dystrophin levels over their baseline values. Increases in dystrophin on Western blot were supported by nominally statistically significant increases from baseline in dystrophin on mass spectroscopy after 20 to 24 weeks of treatment with viltolarsen. Mean dystrophin levels increased from 0.6% (±0.2) of normal at baseline to 4.2% (±3.7) of normal by week 25, with a mean change in dystrophin of 3.7% (±3.8) of normal levels; the median change from baseline was 1.9%.

Several timed function and muscle strength tests were evaluated as secondary endpoints including muscle strength, mobility, and functional exercise capacity as measured by time to stand from supine, time to run/walk 10 meters, time to climb 4 Stairs, North Star Ambulatory Assessment, 6-minute walk test, and quantitative muscle testing. A matched natural history group, provided by the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), served as a control. In the published paper, several of these outcomes were reported as showing improvement or stabilization in the treated cohort whereas the CINRG DNHS external comparator group exhibited a decline (data not shown). (28) The FDA concluded that this analysis did not show any clinically meaningful difference in clinical function at the end of 24 weeks of treatment with viltolarsen 40 and 80 mg/kg/week, compared to natural history. Further, given the variability in the natural history of Duchenne

muscular dystrophy, comparisons to a natural history cohort, even when matched controls are utilized, does not appear reliable. (17)

Komaki et al. (2020) published the results of an open-label phase 1/2 exploratory study conducted in Japan in 16 ambulant and non-ambulant participants aged 5 to 12 years who received viltolarsen 40 or 80 mg/kg/week via intravenous infusion for 24 weeks. (29) An increasing trend in dystrophin expression and exon 53 skipping levels was reported. Mean changes in dystrophin expression (% normal) from baseline to weeks 12 and 24 in the 40 mg/kg group were -1.21 (p=.5136) and 1.46 (p=.1636), respectively. Mean changes in 80 mg/kg group was 0.76 (p=.2367) and 4.81 (p=.0536), respectively.

Table 15. Summary of Trial Characteristics of a Key Randomized Trial of Viltolarsen

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Clemens et al. (2020) (3, 28)	U.S. and Canada	6 (5 in U.S. and 1 in Canada)	2016-2017	• Boys 4 to 9 years (median age 7 years) on a stable corticosteroid regimen for at least 3 months • Diagnosed with DMD, confirmed by a genetic test with exon 53 skipping • Ambulatory, and could complete time to stand from supine, time to run/walk 10 m, and time to climb 4 stairs assessments at screening • Major exclusions[a] • Efficacy assessed based on change from	Part 1 (first 4 weeks): randomized double blind phase Part 2: (20 weeks): open-label viltolarsen 40 mg/kg once weekly (n=8) or 80 mg/kg once weekly (n=8)	Placebo for part 1 External comparator group for timed function and strength evaluations provided by CINRG DNHS and was matched for key enrollment criteria, including age, functional status, geographic location, and glucocorticoid treatment status

				baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at week 25		

CINRG: Cooperative International Neuromuscular Research Group; DMD: Duchenne muscular dystrophy; DNHS: Duchenne Natural History Study; n: number, U.S. United States.

[a] Acute illness as determined by the site investigator (generally upper respiratory tract infection, gastroenteritis, or any febrile illness) 4 weeks prior to first dose, evidence of symptomatic cardiomyopathy, severe allergy or hypersensitivity to study drug, severe behavioral or cognitive problems, any medical findings that would make participation unsafe or impair the assessment of study results or the conduct of the study according to investigator opinion, taking any other investigational drug currently or in the previous 3 months, surgery in the previous 3 months or planned during the study, previous participation in a study that included viltolarsen administration, or positive test results for hepatitis B antigen, hepatitis C antibody, or HIV antibody.

Table 16. Summary of Efficacy Results of a Key Randomized Trial of Viltolarsen

Study	**Mean dystrophin levels**
Clemens et al. (2020) (28)	
N	8
Viltolarsen	Baseline: 0.6% Week 25: 5.9%
Diff (95% CI)	+5.3% (±4.5)
p-value	.01

CI: confidence interval; Diff: difference; N: number.

The purpose of the limitations table (Table 17) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 17. Study Relevance Limitations

Study; Trial	**Population[a]**	**Intervention[b]**	**Comparator[c]**	**Outcomes[d]**	**Follow-Up[e]**
Clemens et al. (2020) (28)				2. Primary endpoint was a physiologic measure (dystrophin level)	

				and correlation with clinical benefit is unknown. 6. Clinically significant difference not supported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Section Summary: Viltolarsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping who receive viltolarsen, the evidence includes a 2-part multicenter study, which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Results of 8 individuals who received a weekly intravenous infusion of viltolarsen 80 mg/kg showed that at week 25, the mean increase in dystrophin protein levels from baseline was 5.3% (±4.5) of normal levels (p=.01). There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. The minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. Outcomes derived from several timed function and muscle strength tests improved among participants treated with viltolarsen compared to a matched natural history control group. However, given the variability in the natural history of Duchenne muscular dystrophy, comparisons to a natural history cohort is not reliable. Further, the clinical relevance of the observed differences is unknown. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with viltolarsen will translate into a clinical benefit to patients. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of viltolarsen in patients with Duchenne muscular dystrophy amenable to 53 skipping.

Casimersen

The clinical development program of casimersen for individuals with Duchenne muscular dystrophy includes a single, ongoing, double-blind, placebo-controlled, multicenter study called ESSENCE, summarized in Table 18.

Table 18. Summary of the Clinical Development Program for Casimersen

Trial	NCT	Phase	Description	N	Design	Status
ESSENCE (4045-301)	NCT02500381	2	Efficacy and safety of casimersen	111	DBRCT (part 1) and open-label (part 2)	Ongoing (unpublished)

DBRCT: double-blind randomized controlled trial; N: number; NCT: national clinical trial.

Pivotal Trial

Trial characteristics and results of the pivotal ESSENCE trial as reported in the FDA prescribing label are summarized in Tables 19 and 20, respectively. The ESSENCE trial was initiated in 2016 with a planned enrollment of 111 participants. The interim analysis reported data from 43 participants who were randomized to receive a once-weekly intravenous infusion of casimersen dosed at 30 mg/kg (n=27) or placebo (n=16). 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. Safety and pharmacokinetic parameters of a subset of 12 participants have been published but are not reported here. (30) As with other FDA approved antisense oligonucleotides (such as eteplirsen, golodirsen, and viltolarsen), no specific safety issues were observed in the limited number of participants who were evaluated in the ESSENCE trial. Most reported treatment emergent adverse events were mild in severity; 2 were related to treatment, and no participants discontinued study drug or reduced dosage due to adverse events. No clinically significant laboratory abnormalities or worsening in electrocardiograms and echocardiograms were noted. (4)

Table 19. Summary of Trial Characteristics of a Key Randomized Trial of Casimersen

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
ESSENCE (4)	Multi-national	66	2016-present	• Males aged 7 to 13 years with DMD and confirmed genetic mutation amenable to exon 45 skipping • Stable pulmonary function • Stable dose of corticosteroids for ≥6 months • Major exclusions[a] • Primary endpoint: Change in 6MWT from	• Part 1 (96 weeks): Casimersen 30 mg/kg (n=not reported) • Part 2 (up to 144 weeks): Casimersen 30 mg/kg (n=not reported)	Part 1 (96 weeks): Placebo (n=not reported)

				baseline to week 96 • Secondary endpoints: Change in 6MWT at week 144, change in dystrophin protein and dystrophin intensity levels at week 48 or 96, and ability to rise independently from the floor, time to loss of ambulation, change in NSAA scores, and change in FVC% predicted at week 96 and 144		

6MWT: 6-minute walk distance; DMD: Duchenne muscular dystrophy; FVC: forced vital capacity; n: number; NSAA: The North Star Ambulatory Assessment

[a] Treatment with gene therapy at any time; previous treatment with DMD experimental treatments within 24 weeks prior to week 1, current or previous treatment with any other experimental treatment (other than deflazacort) within 12 weeks prior to week 1, major surgery within 3 months prior to week 1, presence of other clinically significant illness.

Table 20. Summary of Interim Efficacy Results of a Key Randomized Trial of Casimersen

Study	Placebo	Casimersen
ESSENCE (4)		
N	16	27
Baseline mean dystrophin levels (% of normal)	0.54 (±0.79)	0.93 (±1.67)
Week 48 mean dystrophin levels (% of normal)	0.76 (±1.15)	1.74 (±1.97)
Change from baseline mean	0.22 (±0.49)	0.81 (±0.70)
p-value change from baseline to week 48	<.09	<.001
Between group difference	0.59 (p=.004)	

N: number.

Tables 21 and 22 display notable relevance and design and conduct limitations identified in the study.

Table 21. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
ESSENCE (4)				2. Reported outcome was a physiologic measure (dystrophin level) and correlation with clinical benefit is unknown. 6. Clinically significant difference not supported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 22. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
ESSENCE (4)					1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically	

					important difference	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Casimersen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 45 skipping who receive casimersen, the evidence includes a single, double-blind, placebo-controlled phase 3 trial. An interim analysis conducted at week 48 with data from 46 participants with exon 45 skipping (casimersen, n=27 and placebo, n=16) is available. Compared to those who received placebo, participants who received casimersen demonstrated a statistically significant increase in dystrophin production by 0.59% at week 48 as measured by Western blot. The mean change from baseline to week 48 in dystrophin production was 0.81% versus 0.22% (p=.004) in the casimersen versus placebo arms, respectively. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with casimersen will translate into a clinical benefit to patients.

Summary of Evidence

Eteplirsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes 1 RCT, 1 ongoing, prospective, open-label trial with a concurrent untreated control arm, and multiple post-hoc studies with historical controls. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total participants was selected with 4 participants in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in the 6-minute walk test distance or change in the North Star Ambulatory

Assessment total score between eteplirsen-treated participants and placebo-treated participants at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analyses of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen-treated participants was less compared to historical controls. However, the post-hoc nature of the analyses and the fact that the cohorts were retrospectively identified within the untreated group of participants is of serious concern due to potential selection bias and undermines the robustness of the data. Particularly, the 6-minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus, the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Golodirsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping who receive golodirsen, the evidence includes a 2-part multicenter study which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Results of an interim analysis were based on 25 participants who received a weekly intravenous infusion of golodirsen 30 mg/kg. At week 48, the mean change in dystrophin protein levels was a 0.924% increase from the baseline (1.019% vs. 0.095%; $p<.001$). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with golodirsen will translate into a clinical benefit to patients. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of golodirsen in patients with Duchenne muscular dystrophy amenable to 53 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Viltolarsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 53 skipping who receive viltolarsen, the evidence includes a 2-part multicenter study which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. In 8 participants who received a weekly intravenous infusion of viltolarsen 80 mg/kg, the mean increase in dystrophin protein levels from baseline was 5.3% (±4.5) of normal levels (p=.01) at week 25. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. Outcomes derived from several timed function and muscle strength tests improved among participants treated with viltolarsen compared to a matched natural history control group. However, given the variability in the natural history of Duchenne muscular dystrophy, comparison to a natural history cohort has limited reliability. Further, the clinical relevance of the observed differences is unknown. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with viltolarsen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of viltolarsen in patients with Duchenne muscular dystrophy amenable to 53 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Casimersen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 45 skipping who receive casimersen, the evidence includes a single, double-blind, placebo-controlled phase 3 trial. An interim analysis conducted at week 48 with data for 46 participants with exon 45 skipping (casimersen=27 and placebo=16) is available. Compared to those who received placebo, participants who received casimersen demonstrated a statistically significant increase in dystrophin production by 0.59% at week 48 as measured by Western blot. The mean change from baseline to week 48 in dystrophin production was 0.81% versus 0.22% (p=.004) in the casimersen versus placebo arms, respectively. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with casimersen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of casimersen in patients with Duchenne muscular dystrophy amenable to 45 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Centers for Disease Control and Prevention

In 2010, the U.S. Centers for Disease Control and Prevention convened a Duchenne muscular dystrophy Care Considerations Working Group. In 2010, the Working Group developed care recommendations and updated them in 2018. (31) Their recommendations focus on the overall

perspective on care, pharmacologic treatment, psychosocial management, rehabilitation, orthopedic, respiratory, cardiovascular, gastroenterology and nutrition, and pain issues, as well as general surgical and emergency room precautions. The Centers for Disease Control and Prevention recommended the use of corticosteroids to slow the decline in muscle strength and function in Duchenne muscular dystrophy. The Working Group did not make recommendations on the use of eteplirsen. However, eteplirsen is discussed briefly under the section on "Emerging treatments." (32) In 2016, the Working Group stated that eteplirsen was approved by the U.S. Food and Drug Administration (FDA) for males with the dystrophin gene variant amenable to exon 51 skipping, which is about 13% of the males with Duchenne muscular dystrophy.

American Heart Association

In 2017, a statement from the American Heart Association addressed the treatment of cardiac issues in individuals with any of several neuromuscular diseases, including Duchenne muscular dystrophy. (33) For individuals with Duchenne muscular dystrophy, the Association recommended the use of glucocorticoids, among other medications. The statement does not address the use of eteplirsen. One of the statement's co-authors disclosed being an industry-supported investigator for the drug.

American Academy of Neurology

In 2016, the American Academy of Neurology published an updated practice guideline on the use of corticosteroids for the treatment of Duchenne muscular dystrophy. (34) These guidelines were reaffirmed on January 22, 2022. The Academy does not discuss the use of eteplirsen for Duchenne muscular dystrophy.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review assessed the comparative clinical effectiveness and value of eteplirsen and golodirsen for Duchenne muscular dystrophy in 2019. (19) The Report concludes, "Data on patient-important outcomes with eteplirsen are extremely limited, and studies of dystrophin levels show increases that are of uncertain clinical/biologic importance. There is no high- or moderate-quality evidence demonstrating improvements in function with eteplirsen, as the available long-term data showing potential clinical benefits are observational with matched or historical controls and need to be confirmed in larger, ongoing trials. Furthermore, the main outcome reported, 6-minute walk test, is subject to patient effort, which may lead to less precision in the outcome measure and affect the results of a small, unblinded study. There are no particularly concerning safety signals with eteplirsen but given the small number of patients and short follow-up times, harms could be missed. We consider the evidence to be insufficient ("I"), as certainty of net benefit based on currently available evidence is low."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 23.

Table 23. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Eteplirsen			
Ongoing			
NCT03992430[a]	A Study to Compare Safety and Efficacy of a High Dose of Eteplirsen in Duchenne Muscular Dystrophy (DMD) PATIENTS (MIS51ON)	160	Oct 2026
Unpublished			
NCT02420379[a]	An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy, and Tolerability of Eteplirsen in Early Stage Duchenne Muscular Dystrophy	33	Dec 2018
Golodirsen			
Unpublished			
NCT03532542	An Extension Study to Evaluate Casimersen or Golodirsen in PATIENTS With Duchenne Muscular Dystrophy	171	Jul 2023
Viltolarsen			
Ongoing			
NCT04687020	Long-term Use of Viltolarsen in Boys With Duchenne Muscular Dystrophy in Clinical Practice (VILT-502)	9	Oct 2032
Unpublished			
NCT04060199	Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys With DMD (RACER53)	77	Oct 2023
Casimersen			
Ongoing			
NCT02500381	Study of SRP-4045 and SRP-4053 in DMD PATIENTS (ESSENCE)	229	Oct 2025
Unpublished			
NCT03532542	An Extension Study to Evaluate Casimersen or Golodirsen in PATIENTS with Duchenne Muscular Dystrophy	171	Jul 2023

NCT: national clinical trial.

[a] Denotes industry sponsorship or co-sponsorship.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	96365
HCPCS Codes	J1426, J1427, J1428, J1429

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Other:

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. Medical document combined with content from RX501.122 Golodirsen, RX501.129 Viltolarsen, and RX501.135 Casimersen. Added/updated references 1-4, 25, and 30. Title changed from “Eteplirsen”.
09/15/2024	Reviewed. No changes.
10/15/2023	Document updated with literature review. Coverage unchanged. Added references 11, 21-25; others updated and/or removed.
01/01/2023	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. Added references 17, 23; others updated.
07/01/2020	Document updated with literature review. Coverage unchanged. The following references were added 6, 7, 8, 11, 17-26. Title changed from “Eteplirsen (Exondys 51)”
04/15/2018	Reviewed. No changes.
06/15/2017	New medical document. Eteplirsen (Exondys 51™) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established. Eteplirsen (Exondys 51™) for the treatment of all other indications is considered experimental, investigational and/or unproven.