Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Treatment for Duchenne Muscular Dystrophy

Professional / Institutional
Original Effective Date: January 19, 2017
Latest Review Date: October 8, 2024
Current Effective Date: June 21, 2021

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping	Interventions of interest are: • Eteplirsen	Comparators of interest are: • Continued medical management (e.g., glucocorticoids)	Relevant outcomes include: • Disease-specific survival • Change in disease status • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping	Interventions of interest are: • Golodirsen	Comparators of interest are: • Continued medical management (e.g., glucocorticoids)	Relevant outcomes include: • Disease-specific survival • Change in disease status • Functional outcomes • Health status measures • Quality of life

Populations	Interventions	Comparators	Outcomes
			• Treatment-related mortality • Treatment-related morbidity
Individuals: • With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping	Interventions of interest are: • Viltolarsen	Comparators of interest are: • Continued medical management (e.g., glucocorticoids)	Relevant outcomes include: • Disease-specific survival • Change in disease status • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 45 skipping	Interventions of interest are: • Casimersen	Comparators of interest are: • Continued medical management (e.g., glucocorticoids)	Relevant outcomes include: • Disease-specific survival • Change in disease status • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity

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.

OBJECTIVE

The objective of this evidence review is to determine whether use of antisense oligonucleotides such as eteplirsen, golodirsen, viltolarsen, and casimersen compared with continued medical management improves the net health outcome of individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping.

BACKGROUND

The objective of this evidence review is to determine whether use of antisense oligonucleotides such as eteplirsen, golodirsen, viltolarsen, and casimersen compared with continued medical management improves the net health outcome of individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping.

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.[4,]

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. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

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". The expected date of trial completion is July 2024 and final report submission to the FDA by December 2024.

Casimersen
In February 2021, casimersen (Amondys45™; 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. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

POLICY

The use of antisense oligonucleotides (such as viltolarsen, eteplirsen, casimersen and golodirsen) is considered **experimental / investigational** for all indications, including treatment of Duchenne muscular dystrophy.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created with searches of the PubMed database. The most recent literature update was performed through June 24, 2024.

Evidence reviews 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 review.

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 [1,].

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 review.

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."[5,]

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 yrs (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, language, motor, adaptive, and social-emotional development.	Composite scores are derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100, standard deviation of 15, and range of 40 to 160.	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.
NSAA or an age-appropriate modified NSAA	Measures functional motor abilities. Appropriate for ambulatory children ages >3 yrs 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, can be appropriate for patients as young as 5-6 yrs of age. Performance may increase with time in very young patients	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.[6,7,] Interpretation of 6MWT results is limited

Outcome Measure	Description	Scale	Clinically Meaningful Difference/Comment
	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 during the trial; such patients contribute zero values.		by the variability in testing procedures and patient motivation.
Myometric assessments	Appropriate to measure increase or preservation of muscle strength, and it can be used to provide reliable measurements in children ages 5 yrs 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

Outcome Measure	Description	Scale	Clinically Meaningful Difference/Comment
			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.

REVIEW OF EVIDENCE

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[8,]
STUDY 204	NCT01540409	2	Rollover Study of Study 204 with a follow-up of 4 yr	12	Open-label	Completed and published [9,]
STUDY 301	NCT02255552 (PROMOVI)	3	Treatment of ambulant subjects aged 7 to 16 yrs with Duchenne muscular dystrophy	109	Open-label with concurrent untreated control arm	Completed and published[10,]

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.[11,] 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.[8,] 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.[12,]

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.[12,] 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 ($p<.005$).[8,] 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.[13,]Further, in an exploratory analysis, the FDA found no correlation between dystrophin levels and the 6-minute walk test distance.[12,] 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.[10,] 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.[11,] Results were subsequently published by Mendell et al (2016)[9,] 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[11,] and others[14,] 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.[15,] 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).[16,] Data on matched controls were obtained from prospective natural history studies of more than 400 Duchenne muscular dystrophy participants.[17,] 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.[18,] 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.[19,] 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.[20,] 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.[21,] 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.[11,]

Table 3. Summary of Key Study Characteristics

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	Comparator
Study 201							
Mendell et al (2013)[8,]	U.S.	RCT	1	24 wk	Participants with Duchenne muscular dystrophy ages 7-13 yrs with confirmed deletions amenable to skipping exon 51 and ability to walk 200-400 m on a 6MWT and on glucocorticoids for ≥24 wk	Eteplirsen 30 mg/kg/wk (n=4); Eteplirsen 50 mg/kg/wk (n=4)	Placebo (n=4)
Study 202							
Mendell et al (2016)[9,]	U.S.	Open-label	1	4 yr	All participants from study 201 were enrolled in study 202	Eteplirsen 30 mg/kg/wk (n=6); Eteplirsen 50 mg/kg/wk (n=6)	None
Study 301							
Khan et al (2019)[16,]	U.S.	Open-label, ongoing study[a]	37	96 wk	Participants with Duchenne muscular dystrophy ages 7-16 yrs with confirmed deletions amenable to skipping exon 51 and ability to walk >300 m on a 6MWT and on glucocorticoids for ≥24 wk	Eteplirsen 30 mg/kg/wk (n=12); target is 80 participants	Untreated controls with Duchenne muscular dystrophy not amenable to exon 51 skipping

6MWT: 6-minute walk test; RCT: randomized controlled trial.
[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)[8,]					
All eteplirsen (n=8)	NR	NR	47.3 (3.9)[a]	NR	NR

Study	Mean Percent Change in Dystrophin Level From Baseline (SE)			Mean Change in 6MWT (SE), Meters	
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)				
	Baseline		Week 48	p	
Sarepta et al (2016)	0.16 (0.12)		0.44 (0.43)	.008	

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

a p<.01 vs. baseline.
b Excluding 2 individuals who showed rapid disease progression at week 4 of study.
c p<.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)[9,]										
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 individuals 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[17,]	Number of observations	Baseline Mean	Mean Annual Change (SE) in FVC%	Diff in annual change vs. 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)	<.001

Matched Control/Trials[17,]	Number of observations	Baseline Mean	Mean Annual Change (SE) in FVC%	Diff in annual change vs. Control, 95% CI	P-value
Study 204 (n=20)	117	65.9 (16.6)	-3.66 (0.68)	2.34 (0.77 to 3.90)	.004
Study 301 (n=42)	184	78.5 (15.7)	-3.79 (0.82)	2.21	.017

Adapted from The Institute for Clinical and Economic Review Evidence Report.
CI: confidence interval; FVC%: percent predicted forced vital capacity; 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 the 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)[8,] Study 201				2. Primary endpoint was a physiologic measure (dystrophin level) and correlation with clinical benefit is unknown. 4. Dystrophin measured by IHC staining which only reports presence or absence, vs. Western blot which measures quantity of dystrophin. 6. Clinical significant difference not supported.	
Mendell et al (2016)[9,] Study 202				5. Clinical significant difference for 6MWT was not pre-specified. 6. Clinical significant difference not supported.	
Khan et al (2019)[16,] Study 301				5. Clinical significant difference for percent predicted forced vital capacity was not pre-specified. 6. Clinical 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.
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. Clinical significant difference not prespecified; 6. Clinical 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)[8,] 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 participants in treatment arms who lost ambulation were excluded from 6MWT analysis).	1. Small sample size (each arm had 4 participants).	
Mendell et al (2016)[9,] 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)[16,] Study 301	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		1. High loss to follow-up or missing data (preliminary results of an ongoing study-results from 42 of an expected 109 participants).		

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

The study limitations stated in this table are those notable in the current review; 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 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: 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[13,22,23,]	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; 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.[22,23,] 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[24,22,23,]	U.S., France, Italy, and U.K.	5	2015-2019	• Males aged 6 to 15 yrs (N=25) • 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]	Part 1 (12 ks): Golodirsen escalating dose (n = 8) Part 2 (up to 168 wks): (n = 25)	Part 1 (12 wks): Placebo (n=4) Part 2 (up to 168 wks): Untreated group not amenable to exon 53 skipping (n=24)

DMD: Duchenne muscular dystrophy; 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] 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[2,22,23,]				
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; 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[13,22,23,]				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. Clinical significant difference not prespecified; 6. Clinical 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[13,22,23,]	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[25,]

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).[25,] 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.[13,]

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.[26,] 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)[25,27,]	U.S. and Canada	6 (5 in US 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 baseline in	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

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
				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.
[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)[27,]	
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.

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)[25,]				2. Primary endpoint was a physiologic measure (dystrophin level) and correlation with clinical benefit is unknown. 6. Clinical 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. Clinical significant difference not prespecified; 6. Clinical 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; 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.[28,] 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.[29,]

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

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
ESSENCE[29,]	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 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	• 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)

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
				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; 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[29,]		
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)	

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[29,]				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. Clinical significant difference not prespecified; 6. Clinical 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[29,]					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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[30,]. 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."[31,] 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.[32,] 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.[33,] 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.[15,] 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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

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 No.	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	Nov 2024
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			
Ongoing			
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			

NCT No.	Trial Name	Planned Enrollment	Completion Date
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

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
J1426	Injection, casimersen, 10 mg
J1427	Injection, viltolarsen, 10 mg
J1428	Injection, eteplirsen, 10mg
J1429	Injection, golodirsen, 10 mg

REVISIONS	
01-19-2017	Policy added to bcbsks.com web site 12-20-2016. Policy effective 01-19-2017.
12-29-2017	Description section updated
	Rationale section updated
	In Coding section: ▪ Removed HCPCS Codes: J3490, J3590 ▪ Added HCPCS Code: J1428 (Effective 01-01-2018)
	References updated
03-13-2019	Description section updated
	Rationale section updated
	References updated
04-20-2020	Policy published 03-20-2020. Policy effective 04-20-2020.
	Title revised from "Eteplirsen (Exondys 51) for Duchenne Muscular Dystrophy" to "Eteplirsen (Exondys 51) and Golodirsen (Vondys 53)"
	Description section updated
	In Policy section: ▪ Added Item B "The use of Golodirsen is considered experimental / investigational for all indications, including but not limited to Duchenne muscular dystrophy." ▪ Policy Guidelines removed
	Rationale section updated
	In Coding section: ▪ Added HCPCS Code: J3490
	References updated
09-18-2020	Title Changed from "Eteplirsen (Exondys 51) and Golodirsen (Vondys 53) for Duchenne Muscular Dystrophy" to "Treatment for Duchenne Muscular Dystrophy"
	Description section updated
	In Policy section:

REVISIONS	
	▪ Revised the policy statement to one E/I statement from two E/I statements, which does not change the intent of the policy. TO: "The use of eteplirsen and golodirsen is considered experimental / investigational for all indications, including treatment of Duchenne muscular dystrophy." FROM: "A. The use of eteplirsen is considered experimental / investigational for all indications, including, but not limited to the treatment of Duchenne muscular dystrophy B. The use of Golodirsen is considered experimental / investigational for all indications, including but not limited to Duchenne muscular dystrophy." ▪ Policy Guidelines removed.
	Rationale section updated
	References updated
05-21-2021	Description Section updated
	In the Policy section • Added "antisense oligonucleotides (such as viltolarsen,"
	Rationale Section updated
	In Coding Section Added HCPCS codes J1427 and J1429
	Updated References
06-21-2021	Description Section updated
	In the Policy section • Added "casimersen"
	Rationale Section updated
	Updated References
08-11-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added J1426 ▪ Removed J3490
	Updated References Section
06-27-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
	Updated References Section
10-08-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section

REFERENCES

1. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. Feb 2010; 9(2): 177-89. PMID 19945914
2. Center for Disease Control and Prevention. Muscular Dystrophy: MD STARnet Data and Statistics. 2016; http://www.cdc.gov/ncbddd/musculardystrophy/data.html. Accessed April 26. 2024.
3. Falzarano MS, Scotton C, Passarelli C, et al. Duchenne Muscular Dystrophy: From Diagnosis to Therapy. Molecules. Oct 07 2015; 20(10): 18168-84. PMID 26457695

4. Committee for Medicinal Products for Human Use (CHMP) Assessment Report: Exondys. Published September 20, 2018, Available at https://www.ema.europa.eu/en/documents/assessment-report/exondys-epar-refusal-public-assessment-report_en.pdf. Accessed April 26, 2024.
5. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry. Published February 2018. https://www.fda.gov/media/92233/download. Accessed April 26, 2024.
6. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve. Sep 2013; 48(3): 343-56. PMID 23681930
7. Henricson E, Abresch R, Han JJ, et al. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. PLoS Curr. Jul 08 2013; 5. PMID 23867975
8. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. Nov 2013; 74(5): 637-47. PMID 23907995
9. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. Feb 2016; 79(2): 257-71. PMID 26573217
10. McDonald CM, Shieh PB, Abdel-Hamid HZ, et al. Open-Label Evaluation of Eteplirsen in Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping: PROMOVI Trial. J Neuromuscul Dis. 2021; 8(6): 989-1001. PMID 34120909
11. Food and Drug Administration. FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisory Committee Meeting, April 25, 2016. NDA 206488. Eteplirsen. 2016; https://www.fda.gov/media/97306/download. Accessed April 26, 2024.
12. Woodcock J, Dunn B. FDA Presentations for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. 2016; https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-25-2016-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-04242016. Accessed April 26, 2024.
13. Center for Drug Evaluation and Research. Application Number: 206488orig1s000. Summary Review. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000Approv.pdf. Accessed April 26, 2024.
14. Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. Dec 13 2016; 316(22): 2357-2358. PMID 27775756
15. Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Institute for Clinical and Economic Review. https://icer.org/wp-content/uploads/2020/10/ICER_DMD-Final-Report_081519-2-1.pdf. Accessed April 26, 2024.
16. Khan N, Eliopoulos H, Han L, et al. Eteplirsen Treatment Attenuates Respiratory Decline in Ambulatory and Non-Ambulatory Patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2019; 6(2): 213-225. PMID 30856119
17. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. Feb 03 2018; 391(10119): 451-461. PMID 29174484

18. Kinane TB, Mayer OH, Duda PW, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. J Neuromuscul Dis. 2018; 5(1): 47-58. PMID 29278896
19. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. Medicine (Baltimore). Jun 2019; 98(26): e15858. PMID 31261494
20. Mitelman O, Abdel-Hamid HZ, Byrne BJ, et al. A Combined Prospective and Retrospective Comparison of Long-Term Functional Outcomes Suggests Delayed Loss of Ambulation and Pulmonary Decline with Long-Term Eteplirsen Treatment. J Neuromuscul Dis. 2022; 9(1): 39-52. PMID 34420980
21. Iff J, Zhong Y, Tuttle E, et al. Real-world evidence of eteplirsen treatment effects in patients with Duchenne muscular dystrophy in the USA. J Comp Eff Res. Sep 2023; 12(9): e230086. PMID 37610303
22. Prescribing Label: VYONDYS 53 (golodirsen) injection, for intravenous use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf. Accessed April 26, 2024.
23. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. Neurology. May 26 2020; 94(21): e2270-e2282. PMID 32139505
24. Center for Drug Evaluation and Research. Application Number: 212154Orig1s000. Summary Review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212154Orig1s000SumR.pdf. Accessed on April 26, 2024.
25. 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. Aug 01 2020; 77(8): 982-991. PMID 32453377
26. Komaki H, Takeshima Y, Matsumura T, et al. Viltolarsen in Japanese Duchenne muscular dystrophy patients: A phase 1/2 study. Ann Clin Transl Neurol. Dec 2020; 7(12): 2393-2408. PMID 33285037
27. Prescribing label VILTEPSO (viltolarsen) injection, for intravenous use. Initial U.S. Approval: 2020. Available at https://www.viltepso.com/prescribing-information. Accessed April 26, 2024.
28. Wagner KR, Kuntz NL, Koenig E, et al. Safety, tolerability, and pharmacokinetics of casimersen in patients with Duchenne muscular dystrophy amenable to exon 45 skipping: A randomized, double-blind, placebo-controlled, dose-titration trial. Muscle Nerve. Sep 2021; 64(3): 285-292. PMID 34105177
29. Prescribing Label: Amondys 45 (casimersen) injection, for intravenous use. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213026lbl.pdf. Accessed on April 26, 2024.
30. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. Apr 2018; 17(4): 347-361. PMID 29395990
31. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. Mar 2018; 17(3): 251-267. PMID 29395989

32. Feingold B, Mahle WT, Auerbach S, et al. Management of Cardiac Involvement Associated With Neuromuscular Diseases: A Scientific Statement From the American Heart Association. Circulation. Sep 26 2017; 136(13): e200-e231. PMID 28838934
33. Gloss D, Moxley RT, Ashwal S, et al. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. Feb 02 2016; 86(5): 465-72. PMID 26833937