Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value

Evidence Report

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Prepared for

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Grace Lin served as the lead author for the report and wrote the background, other benefits, and contextual considerations sections of the report. Foluso Agboola was responsible for the oversight of the systematic review and authorship of the comparative clinical effectiveness section with the support of Ifeoma Otuonye and Noemi Fluetsch. Varun Kumar and Sumeyye Samur were responsible for oversight of the cost-effectiveness analyses and Sumeyye Samur developed the budget impact model. Catherine Koola authored the section on coverage policies and clinical guidelines. Surrey Walton, Nicole Boyer, and Danny Quach developed the cost-effectiveness model and authored the corresponding sections of the report. David Rind, Rick Chapman, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo and Maggie O'Grady for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals are responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/dmd-stakeholder-list/.

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List of Acronyms Used in this Report

6MWT	6-Minute Walk Test
AAN	American Academy of Neurology
AE	Adverse event
AWP	Average wholesale price
BCBSFL	Blue Cross Blue Shield of Florida
BCBSMA	Blue Cross Blue Shield of Massachusetts
BCBSMI	Blue Cross Blue Shield of Michigan
BCBSNC	Blue Cross Blue Shield of North Carolina
BCBSNJ	Blue Cross Blue Shield of New Jersey
BCBSTN	Blue Cross Blue Shield of Tennessee
BMD	Becker muscular dystrophy
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DMD	Duchenne muscular dystrophy
DMDSAT	Duchenne muscular dystrophy Functional Ability Self-Assessment Tool
DRG	Diagnosis-related group
FDA	Food and Drug Administration
FVC	Forced vital capacity
FVC%p	Predicted forced vital capacity
FSS	Federal Supply Schedule
HCSC	Health Care Service Corporation
LY	Life year
MRC	Medical Research Council
mRNA	Messenger ribonucleic acid
MDA	Muscular Dystrophy Association
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
PPMD	Parent Project Muscular Dystrophy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	Person-year
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
SPEC	Tufts Medical Center Specialty Drug Evidence and Coverage Database
UIC	University of Illinois at Chicago
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force

Executive Summary

Background

Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by one of more than 2000 mutations in the dystrophin gene (*DMD*) that result in progressive loss of muscle function due to the loss of expression of the dystrophin protein to less than 3% of normal.[1] It is the most common pediatric muscular dystrophy with a prevalence of 1 in 3,500-5,000 live male births, or about 400 to 600 boys per year in the United States (US).[2] The majority of patients (70%) have a single or multi-exon deletion or duplication and severity of disease appears to vary with mutation, resulting in a heterogeneous population with differing rates of progression.[3,4] Rarely, females who are carriers of a *DMD* mutation can also be symptomatic.[5]

Signs of DMD usually occurs in early childhood, with a mean age of symptom onset of 2.5 years. Symptoms include muscle weakness, clumsiness, and difficulty going up and down the stairs, and untreated children with DMD usually progress to a loss of ambulation by age 10.[6] Children may also have developmental delay and behavioral issues, as well as impaired growth, delayed puberty, and gastrointestinal complications (e.g., dysphagia and gastroparesis). Orthopedic complications such as contractures and scoliosis occur in most patients, typically after loss of ambulation. Bone health is a major long-term problem, as osteoporosis frequently occurs in the later stages of the disease, with a high risk of fracture. Because of the significant disability caused by DMD, quality of life is diminished and caregiving burden is high. Fatal respiratory or cardiac complications commonly develop in the second or third decade of life, with many deaths occurring in the setting of an acute infection such as pneumonia or after surgery.[7,8] However, treatments such as corticosteroids, assisted ventilation, spinal surgery, and management of cardiomyopathy-related heart failure have led to delays in disease progression such that some patients are now surviving into their 30s or 40s.[4]

Since DMD is a degenerative disorder that affects multiple organ systems, care of DMD patients is provided by a multispecialty team, typically led by a neuromuscular specialist. Treatment for DMD currently includes supportive care and medications such as corticosteroids and exon-skipping therapies (Table ES1). DMD is a costly disease, particularly as the disease progresses – annual medical costs are estimated to be around $22,500 and can increase as much as five-fold due to increased health care utilization as patients lose the ability to walk.[9-13]

Table ES1. Drug Therapies for DMD Discussed in the Report

Drug (Brand Name)	Manufacturer	US FDA Approval Date	Class of Drug	Method of Delivery	Approved Population
Deflazacort (Emflaza®)	PTC Therapeutics	February 2017	Corticosteroid	Oral	DMD patients 2 years and older
Eteplirsen (EXONDYS 51™)	Sarepta Therapeutics	September 2016	Exon-skipping of exon 51	Intravenous	DMD patients with mutations amenable to exon 51 skipping
Golodirsen	Sarepta Therapeutics	N/A	Exon-skipping of exon 53	Intravenous	N/A

DMD: Duchenne muscular dystrophy, US FDA: United States Food and Drug Administration

The natural history of DMD is such that patients have progressive muscle degeneration and weakness, leading to a loss of function, and *supportive care* is integral to treatment of the disease. Physical and occupational therapy are key interventions to maintain ambulation, minimize deformity, optimize respiratory function, and maintain skin integrity.[14] Additionally, patients may progress to needing assistive or mobility devices such as orthotics, power wheelchairs, and other adaptive equipment to maintain function. Home renovations and vehicle modifications may also be necessary. Finally, as respiratory muscles weaken, non-invasive and then invasive assisted ventilation may become necessary.

The mainstay of drug therapy in DMD is *corticosteroids*, including prednisone and deflazacort (Emflaza®, PTC Therapeutics). The exact mechanism of treatment is unknown, but likely includes anti-inflammatory and immunomodulatory effects. While prednisone does not have a US Food and Drug Administration (FDA) indication specific for DMD, it is widely used for treating the disease. Deflazacort is a glucocorticoid prodrug whose active metabolite acts on the glucocorticoid receptor, and while it was first licensed for use overseas in the 1980s, it was not approved by the FDA for treatment of DMD until February 2017 and is marketed by PTC Therapeutics. Initiation and length of treatment with corticosteroids are individualized based on age, functional status, and pre-existing risk factors for adverse effects, but treatment is rarely started prior to the age of 5.[14] There is a lack of consensus on the optimal dosing regimens (e.g., daily, weekly, weekend-only, and intermittent dosing have been used) and also on use after loss of ambulation. Due to differences in the chemical structure between prednisone and deflazacort, there may be differences in tolerability between the two drugs.

Exon-skipping therapies are a new class of drugs that target dystrophin pre-messenger ribonucleic acid (mRNA) and induce skipping of mutated exons of the *DMD* gene that disrupt downstream protein synthesis and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin that may be beneficial in slowing progression of the disease, though clinical correlation has yet to be established.[15,16] Eteplirsen (EXONDYS 51™) was developed by Sarepta Therapeutics and was the first exon-skipping therapy to be approved by the

FDA; it was approved in September 2016 for DMD patients with mutations amenable to skipping of exon 51 (estimated to be approximately 13% of the DMD population.[17] The FDA label states, "A clinical benefit of EXONDYS 51 has not been established." Eteplirsen is delivered as a weekly intravenous infusion. Golodirsen (SRP-4053) has been developed by Sarepta Therapeutics for patients with mutations amenable to exon 53 skipping, estimated to be 9% of the DMD population. Golodirsen is also delivered weekly via intravenous infusion and is under evaluation for accelerated approval by the FDA, with an expected decision date in August 2019.

Insights Gained from Discussions with Patients and Patient Groups

Caregivers (most commonly parents) described the physical, financial, and emotional tolls of caring for children with DMD, from receiving the life-changing diagnosis to trying to maximize daily life and function as the disease progresses. Caregivers and patient groups highlighted several concerns related to caring for DMD patients. Access and cost of treatment were of major concern, particularly with exon-skipping therapies. Additionally, prior to approval in the US, deflazacort was available to be imported for approximately $1,000 (US dollars) per year. Although many insurers are now covering deflazacort after its approval, leading to potentially increased access and decreased financial burden, insurers often require prior authorization and/or demonstration of failure of prednisone, which creates an additional barrier for patients to obtain the medication.

Financial burdens outside of medical costs that are not covered by insurance (e.g., obtaining wheelchair-accessible transportation, costs of renovations to make homes accessible, travel costs to access specialty care) were often mentioned by caregivers/parents as a major concern. Many caregivers reported spending significant amounts of time navigating the insurance system, for both treatment approval and to obtain equipment such as wheelchairs, and worried that there could be significant financial and health consequences due to insurance-related delays.

The high caregiving burden for patients with DMD was often mentioned, including the anxiety, depression, and isolation that can result from caring for a child (or children) with a severe illness. Caregiver burden was noted to increase when children lost the ability to ambulate and also when upper extremity mobility was lost, as these events represent the loss of independence for patients, resulting in the need for more assistance from caregivers. Thus, delaying loss of ambulation and upper extremity function for as long as possible was mentioned as important patient-centered outcomes. Additionally, weight gain was cited as an important side effect for patients with DMD treated with corticosteroids, as excessive weight gain could lead to both physical and psychological harm for DMD patients, including greater difficulty with ambulation, increased risk of fractures, increased difficulty for caregivers to lift and transfer patients, and impaired sense of well-being.

Caregivers and patient groups expressed concern that research studies did not include broad enough populations, given the heterogeneity of the DMD population, and that a lack of natural

history data impaired the community's ability to accurately assess the effects of interventions. They also cited a lack of validated outcome measures in clinical trials that adequately reflect function in the context of daily life activities (e.g., outcome measures that assess muscle strength in the context of daily life activities, not just on standardized tests), and that lack of such measures may lead to an underestimation of a drug's benefit, as maintenance of activities of daily living may be an important indicator of independence. Furthermore, "improvement" should also include stabilization and/or slowed decline, as preservation of function and independence are of great importance to patients and their caregivers. Patient groups suggested that non-traditional sources of data, such as videos, may be important in capturing and more accurately assessing the full spectrum of treatment benefit, and that validation of video data should be encouraged. Video data are further discussed in Controversies and Uncertainties in Section 3.

Additionally, while they hoped that new breakthrough treatments would help improve quality of life for patients with DMD, particularly by improving or stabilizing functional status and independence, parents were also concerned about the potential side effects, durability, and high cost of such therapies.

Comparative Clinical Effectiveness

We evaluated the comparative clinical effectiveness for the treatment of DMD of the corticosteroid deflazacort compared to prednisone, and of the exon-skipping therapies, eteplirsen and golodirsen, each in addition to corticosteroids and supportive care compared with corticosteroids and supportive care alone. We identified three randomized controlled trials (RCTs) and seven observational studies that assessed the efficacy of deflazacort versus prednisone; two RCTs (one Phase IIb and one ongoing Phase III), one open-label extension, and one single-arm study for eteplirsen; and one Phase I/IIb RCT for golodirsen. Due mainly to differences in study design and outcomes measured, we did not perform meta-analysis or network meta-analysis to quantitatively compare the drugs to each other. Instead, we summarized our review of each drug below.

Corticosteroids

Evidence comparing deflazacort and prednisone is somewhat limited by potential selective reporting and few high-quality trials. It is possible that motor outcomes including time to loss of ambulation may be better with deflazacort, but results were inconsistent across and within trials, and this is uncertain. Undesired weight gain appears to be greater with prednisone than deflazacort, while cataract formation and reduction in growth appear to be greater with deflazacort. Evidence on other important harms is inadequate to come to definite conclusions and overall does not appear to clearly favor either deflazacort or prednisone.

Clinical Benefits

Systematic reviews have demonstrated at least medium-term benefits to treating patients with DMD with corticosteroids.[18] Evidence comparing deflazacort and prednisone is somewhat limited by potential selective reporting and few high-quality trials. The three RCTs were of varying quality.[19-21] The largest trial (Griggs 2016),[19] which was rated as good quality, was a multicenter, Phase III RCT conducted in 196 boys (aged 5-15 years) with DMD. Participants were randomized to receive either deflazacort (0.9 mg/kg), prednisone (0.75 mg/kg), or placebo, and followed for 52 weeks. The two other RCTs (Karimzadeh 2012 and Bonifati 2000) were smaller studies of fair or poor quality.[20,21] We also included seven observational studies comparing deflazacort to prednisone in our review.[22-28]

Muscle Strength

Two RCTs (Griggs 2016 and Bonifati 2000) reported change in muscle strength as an outcome, using the Medical Research Council (MRC) scale. Although Griggs 2016 found an increase in muscle strength in both the deflazacort and prednisone groups compared with placebo,[19] both trials found no significant difference in muscle strength between the deflazacort and prednisone groups after one year of treatment.[19,21]

Motor Function

All three RCTs (Griggs 2016, Karimzadeh 2012, Bonifati 2000) and three observational studies (Shieh 2018, McDonald 2019, Balaban 2005) reported changes in motor function in patients on corticosteroids. Functional outcomes reported in these trials differed, but included measures such as time from supine to standing, time to climb four stairs, time to run or walk 30 feet or 10 meters, or 6MWT, either separately or as a composite score. Results were mixed, with two of the RCTs (Griggs 2016, Karimzadeh 2012) showing statistically significant improvement favoring deflazacort at 12 months in some outcomes (time to climb four stairs, composite motor function outcome), [19,20] but one trial (Bonifati 2000) showed no statistically significant differences in motor function between patients treated with deflazacort or prednisone at 12 months.[21] In the observational trials, point estimates generally favored deflazacort, however, these were often not statistically significant, and the outcomes varied across measures of function.

Ambulation/Loss of Ambulation

Three observational studies (McDonald 2018, Bello 2015, Kim 2015) assessed loss of ambulation. Two studies (McDonald 2018, Bello 2015) found that treatment with deflazacort significantly delayed loss of ambulation by around three years compared with prednisone.[24,27] One study (Kim 2015) found very little difference in mean age at loss of ambulation with either short-term or long-term deflazacort or prednisone use.[26]

Pulmonary Function

Two RCTs (Griggs 2016, Karimzadeh 2012) and one observational study (Balaban 2005) assessed pulmonary function. None of the trials found any significant differences in pulmonary function between the deflazacort- and prednisone-treated groups.

Harms

The majority of adverse events (AEs) reported in the RCTs were mild to moderate, and included weight gain, Cushingoid appearance, hirsutism, and behavior changes. Three observational studies reported long-term safety data related to deflazacort and prednisone over four to 10 years of treatment,[24,27,28] and similarly found that weight gain, Cushingoid appearance, behavior changes, growth delays, fractures, and cataracts were the most frequently observed AEs. Results are summarized in Table ES2 and ES3.

The difference in chemical structure between deflazacort and prednisone suggest that there could be differences in tolerability between the two drugs. Our review found that patients treated with deflazacort had less weight gain and fewer weight-related AEs than those treated with prednisone. Cataract formation and growth delays were more frequently reported in deflazacort-treated patients than those treated with prednisone. Risk of first fracture also appeared to be higher in deflazacort-treated patients.

Table ES2. RCTs Comparing AEs of Deflazacort (DFZ) to Prednisone (PRED) at 52 Weeks

Trial	Arm	N	Death, %	D/C due to AEs, %	Cushingoid, %	Weight Gain, %	Hirsutism, %	Behavior Change, %	Cataracts, %
Griggs 2016	DFZ	68	2	1.5	60	28	35	9	4.4
	PRED	63	2	5	78	35	44	14	1.6
Karimzadeh 2012	DFZ	14	NR	0	NR	NR	NR	NR	0
	PRED	12	NR	33	NR	NR	NR	NR	0
Bonifati 2000	DFZ	9	NR	0	55	11	55	66	22
	PRED	9	NR	11	50	15	50	62	11

AEs: adverse events, D/C: discontinuation, N: total number, NR: not reported

Table ES3. Long-Term AEs of Deflazacort and Prednisone from Observational Studies

Trial/Duration	Intervention	N	PY	Weight Gain, %	Cushingoid, %	Behavior Change, %	Growth Delay, %	Fracture, %	Cataracts, %
McDonald* 10 years	Deflazacort	107	877	5	6	3	5	1	3
	Prednisone	40	191	14	9	6	4	3	<1
Bello 3.8 Years ± 1.8 Years	Deflazacort	94	NR	63	72	33	60	25‡	29
	Prednisone	80	NR	67	50	30	27	22‡	5
Balaban 2005† 7 years	Deflazacort	12	NR	0	NR	8	NR	8	17
	Prednisone	18	NR	16	NR	17	NR	6	0

AE: adverse event, N: total number, NR: not recorded, PY: person-years
*% calculated as number of side effect/total person-years exposure
†Reports only serious AEs
‡Low Bone Mineral Density or Fracture

Exon-Skipping Therapies

Eteplirsen and golodirsen treatment results in very small increases in dystrophin. Extremely limited randomized data for eteplirsen did not show improvements in the 6MWT compared with placebo. No functional outcome results have been reported for golodirsen. Observational data comparing open label eteplirsen to matched or historical controls raise the possibility of improvements in motor and pulmonary function, including time to loss of ambulation. Harms of eteplirsen appear to be minor. No safety data were available to report for golodirsen.

Clinical Benefits

Evidence for the efficacy of eteplirsen and golodirsen are drawn from small studies in patients with DMD with mutations amenable to exon 51 skipping (eteplirsen) and exon 53 skipping (golodirsen) therapies. For eteplirsen, we identified four studies, including a Phase IIb RCT with 12 patients, two open-label studies with follow-up of two to four years to assess ongoing safety and efficacy, and one ongoing Phase III study.[29-31] For golodirsen, we identified one ongoing two-part Phase I/II RCT, with part one as a placebo-controlled, dose escalation trial of 12 patients, and part two as an open-label extension of 25 patients (12 from the original trial and 13 newly recruited patients).[32] The main efficacy outcome was increase in level of dystrophin-positive fibers on muscle biopsy. Secondary outcomes in the eteplirsen trials included 6MWT, loss of ambulation, and pulmonary function; no functional outcomes have been reported for golodirsen.

Dystrophin Production

Treatment with both eteplirsen and golodirsen result in small increases in dystrophin level in DMD patients. For eteplirsen at the 30 mg/kg dose, there was a 23% increase in the percent of

dystrophin positive muscle fibers compared with a loss of 4% in the placebo groups after 24 weeks of treatment, although the actual dystrophin levels were very low, even in follow-up studies (0.93% of dystrophin in healthy subjects after 180 weeks of treatment).[29,33] In another study, 13 patients treated with eteplirsen 30 mg/kg underwent muscle biopsy at baseline and after 48 weeks of treatment.[34,35] Among the 12 patients with evaluable results, mean dystrophin levels increased from 0.16% of the level in healthy subjects to 0.44% the level of healthy subjects (change of 0.28% of normal; p=0.008).

Similar results were seen with golodirsen, with an absolute increase of mean dystrophin levels of 0.918% to just over 1% of normal in patients treated for 48 weeks.[32]

Motor Function/Ambulation/Pulmonary Function

Functional outcomes for eteplirsen were drawn from both the randomized trial and open-label extensions, where 12 patients treated with eteplirsen were matched with historical controls (data obtained from DMD registries), for up to four years of follow-up. In the RCT, all patients, including those treated with eteplirsen had a reduction in 6MWT distance from baseline (-0.3 meters & -128 meters in 50 mg/kg & 30 mg/kg doses of eteplirsen, respectively vs. -26 meters in the placebo group); however, the investigators noted that the large decline in the 30 mg/kg dose was due to two patients who had rapidly progressive disease.[29]

Compared with historical controls, at four years, patients treated with eteplirsen showed less decline in the 6MWT (difference of 162 meters [p=0.0005]), and only 17% of patients lost ambulation during that period, compared with 85% loss of ambulation in the control group.[30] In terms of pulmonary function, patients treated with eteplirsen had a statistically significant slower annual rate of decline in percent predicted forced vital capacity (FVC) than historical controls, with a mean annual decline of 2-4% compared with 6% in the historical control group.[31]

Harms

Harms of the exon-skipping therapies appear to be limited. The majority of AEs observed in the clinical trials of eteplirsen were considered to be mild to moderate, and included procedural pain, incision site hemorrhage or hematoma, balance disorder, hypokalemia, vomiting, bladder disorder, bone pain, and contact dermatitis.[34] There were no AEs leading to discontinuation of the drug, and no deaths were reported.[34] No safety data were reported for golodirsen.

Controversies and Uncertainties

Although there is evidence that corticosteroid treatment is beneficial for DMD patients, the optimal dosing, dosing regimen, and duration of therapy remain unclear. Relatively small clinical trials have provided short-term efficacy data, even though long-term use of corticosteroids is the norm. There

are few trials evaluating prednisone and deflazacort in a head-to-head comparison and the majority of the long-term data comparing the two drugs is from observational studies that may be subject to bias, including uncertainty about the natural history of the disease, lack of consistent dosing and outcomes measures, and selection bias based on the fact that deflazacort was not approved in the US until 2017; patients who could afford to import the drug from overseas may have differed systematically in ways that may affect outcomes.

The data for exon-skipping therapies consist primarily of surrogate outcomes (e.g., dystrophin levels) from very small trials. While the use of surrogate outcomes is often necessary in evaluating a treatment for an ultra-rare disease, this does not mean that a small improvement in a surrogate measure, without convincing human or animal evidence that the surrogate improvement is potentially clinically important, should be considered appropriate evidence for evaluating a therapy, even for an ultra-rare condition. The threshold for dystrophin expression sufficient for meaningful clinical improvement has not yet been defined. Furthermore, there is limited or no evidence demonstrating improvements in function, as comparison with historical controls with conditions such as DMD can be confounded or effort-dependent. Thus, the clinical efficacy of exon-skipping therapies is still unclear.

Although many trials have used standard functional outcomes such as the 6MWT to gauge efficacy of treatment, it is not clear whether these outcomes fully characterize the effects of drug therapy, as there appears to be a gap between currently reported trial outcomes and video evidence shared by patients. For example, videos of patients on eteplirsen appear to show clinical improvement in function that was not reflected in the clinical trial outcomes. Video evaluation has the potential to give a more complete picture of functional status by allowing for observation not only of whether a patient can perform a specific task, but also how the task is being completed, and progression over time. However, until these video outcomes are validated and applied consistently across trials, their use remains limited.

Summary and Comment

As discussed elsewhere in the report, ICER acknowledges that generating high-quality evidence for emerging treatments for ultra-rare diseases can be challenging.

Corticosteroids

Corticosteroids appear to be effective treatments for DMD patients, potentially increasing muscle strength, improving motor function and delaying loss of ambulation. However, whether there are significant differences in outcomes between patients treated with deflazacort compared with prednisone is less clear, as comparative evidence is limited and potentially confounded. Deflazacort may have greater benefits on motor function and delay of loss of ambulation, although not all data are consistent, and the size of the benefit may be small. The primary interest in deflazacort has

been around reduced harms. Most trials reported similar AE rates between deflazacort and prednisone; however, data suggest that deflazacort may cause less weight gain but also reduced growth, increased cataract formation, and increased risk of fracture compared with prednisone. Overall, given the evidence, we have moderate certainty that deflazacort has comparable or better net health benefits compared with prednisone (C+).

Exon-Skipping Therapies

Data on the exon-skipping drugs is extremely limited and randomized trial benefits are limited to the surrogate outcome of dystrophin levels. The small increases in dystrophin levels seen in the RCTs are of uncertain clinical significance. Observational studies comparing outcomes with historical controls have suggested potential functional benefits with eteplirsen, but these data may be confounded and effort-dependent. Based on the current evidence, there are no particularly concerning safety issues with either drug, but given the small numbers of patients and limited follow-up, harms could be missed. We considered the data for eteplirsen and golodirsen to be insufficient ("I").

Long-Term Cost Effectiveness

Changes that have been made in this section of the report since the draft evidence report include corrected values in Table ES4. Two of the original annual drug cost values were reported incorrectly due to arithmetic errors, although this had no effect on downstream calculations or results as they were independent calculations. Also, the incremental cost effectiveness ratios for deflazacort are substantially lower (more favorable) than in the draft report. This was due primarily to updating values for utilities that had been too high for the non-ambulatory health states in the draft report. The revised results did not change the conclusions of the report.

Overview and Methods

The objective of this economic evaluation was to assess the lifetime cost-effectiveness of deflazacort, eteplirsen, and golodirsen for treating patients diagnosed with DMD in the US. Specifically, deflazacort plus supportive care was compared to prednisone plus supportive care. Eteplirsen was evaluated as add-on therapy to corticosteroids plus supportive care versus corticosteroids plus supportive care alone. Since the societal costs associated with DMD were estimated to be substantial relative to the condition's health care sector costs for prednisone and deflazacort, the base-case analyses for deflazacort were reported from health care and modified societal perspectives, aligning with ICER's Value Assessment Framework for Ultra Rare Diseases. For eteplirsen, there was insufficient evidence to model specific treatment effects; therefore threshold-type scenario analyses were performed using potential treatment effects with current prices to assess potential cost-effectiveness. While golodirsen was also considered, in the absence

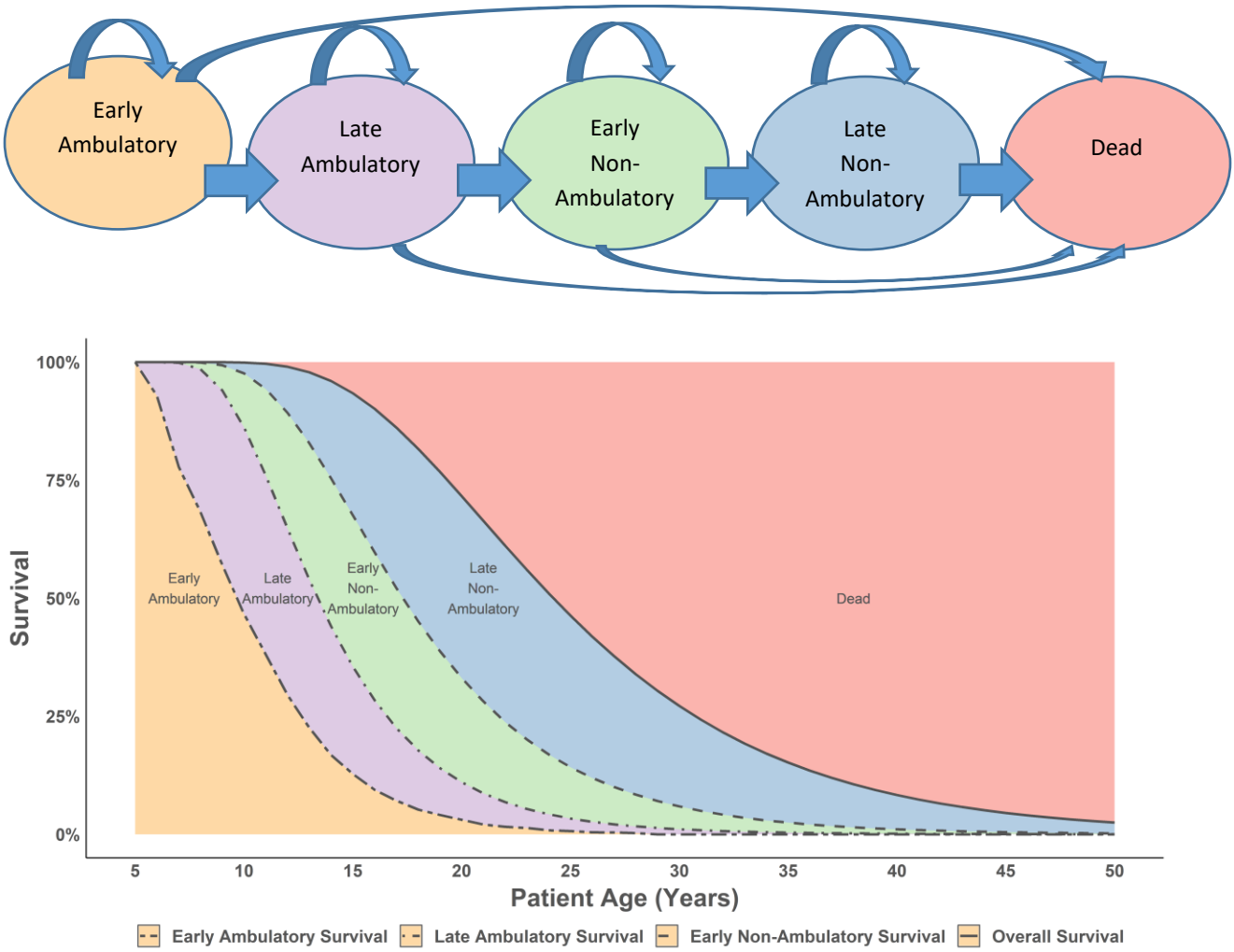
of a treatment effect or price for this therapy, an economic analysis specific to golodirsen was not conducted.

The modeled population consisted of children diagnosed with DMD, with diagnosis and treatment commencing at age five. All comparative treatments were assumed to be given over a lifetime in accordance with the ICER Reference Case. The model incorporated annual estimates of costs and utility scores associated with each health state for US patients from a prior survey.[10] Costs and outcomes were discounted at 3% per year. The primary outcomes of the model were discounted lifetime total costs, quality-adjusted life years (QALYs), and life years (LYs). Uncertainty was assessed via deterministic one-way sensitivity analyses, scenario analyses, and probabilistic sensitivity analysis.

A five-state partitioned survival model was developed for this evaluation, informed by key clinical trials, cohort studies, and prior relevant studies related to economic modeling in DMD.[24,36-40] The five health states were early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory, and death. Children entered the model in the early ambulatory health state at age five. The baseline survival curves that provided the age-dependent proportions of patients in each health state were based on a prior comprehensive analysis of international clinical trial data involving steroid treatment for DMD, and another prior published model in DMD that incorporated these same health states.[36,37]

The structure of the model is outlined in Figure ES1 below.

Figure ES1. Model Framework



There were several key assumptions made in the development of the base-case model.

- Treatment effects were modeled using direct rightward shifts (i.e., parallel shifts) in all survival curves, such that treatments were assumed to consistently delay all stages of progression of the disease.
- In the absence of trial-based treatment efficacy differences between prednisone and deflazacort,[19-21] a favorable, upper-bound, treatment effect of three years was applied to deflazacort.[24] Serious adverse events (SAEs: weight gain, Cushingoid, fractures, cataracts) related to prednisone and deflazacort each resulted in a disutility of 0.05 for the relevant proportion of patients in each annual cycle. This assumption again was favorable to deflazacort as it likely represents an upper-bound disutility and given that deflazacort is associated with fewer SAEs overall.

Drug costs used in the model are shown in Table ES4 below. The dose varies by weight such that annual costs will on average vary by patient age. Annual costs for a 40-kilogram (kg) patient are included in Table ES4 which are close to the average dose over the lifetime horizon in the model.

Table ES4. Drug Costs Used in the Model

Intervention (Dosage)	Cost per mg	Annual Treatment Cost	Source
Prednisone (0.75 mg/kg/day)	$0.05/mg	$550*	Red Book, 2019 [41]
Deflazacort (0.9 mg/kg/day)	$6.19/mg	$81,400*	Federal Supply Schedule, 2019[42]
Eteplirsen 100 mg/2mL (50 mg/mL) 500 mg/10mL (50 mg/mL) (30 mg/kg per week)	$16/mg	$1,002,000*	Red Book†[41]
Golodirsen	N/A	N/A	

AWP: average wholesale price, FSS: Federal Supply Schedule, kg: kilogram, mg: milligram, mL: milliliter, N/A: not applicable

*These estimates are for a 40 kg patient. Actual costs in the model will vary by expected weight based on the patient's age.

†Marked-up price is calculated as AWP-(15%*AWP) when the drug is administered at a hospital/physician's office.

The supportive care non-drug health care costs were sourced from a previous study (see Table 4.6 and Table 4.7 in Section 4 for the costs by category).[10] Health state utilities were obtained from this same study that included data on Health Utility Index scores for US DMD patients and caregiver utilities elicited from the EuroQol EQ-5D-3L[10] (See Table 4.3). Age-dependent mortality for patients with DMD was estimated based on data on age at loss of ambulation and survival data in the US (MD Star*net*), and the modeled mortality in a prior DMD analysis.[36] In terms of AEs, the base-case analysis comparing deflazacort and prednisone considered rates of weight gain, Cushingoid appearance, behavioral change, cataracts, and fractures (see Table 4.2). There were no reported significant AEs for eteplirsen; therefore, none were included in the model.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report and supplemental appendix materials. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Results

The base-case results for incremental cost-effectiveness ratios comparing deflazacort to prednisone represent cost-utility results that are well beyond the range of commonly accepted thresholds of $50,000 to $150,000 per QALY despite highly favorable assumptions about treatment effects being incorporated in the model (see Table ES5). Results of the cost per LY gained analyses were similar to the results seen in the cost per QALY analyses.

Table ES5. Base-Case Incremental Cost-Effectiveness Ratios for Deflazacort with Supportive Care Compared to Prednisone with Supportive Care

Treatment	Cost per QALY Gained	Cost per LY Gained	Cost per Additional Year in Ambulation
Deflazacort Compared to Prednisone Health Sector Perspective	$344,000	$361,000	$250,000
Deflazacort Compared to Prednisone Modified Societal Perspective	$371,000	$390,000	$269,000

QALY: quality adjusted life year; LY: life year

The incremental cost-effectiveness ratios in the modified societal perspective are slightly higher (less favorable) relative to the health care sector perspective's ratios because they include broader societal perspective costs of supportive care such as informal care and indirect cost of the illness during the increased years of ambulation for deflazacort. One-way sensitivity analyses results showcased that changes to treatment effect, patient utility in the early ambulatory state, and the drug cost of deflazacort influenced model results the most. Results of the probabilistic sensitivity analysis showed that at a $150,000 per QALY threshold, deflazacort had less than a 1% probability of being cost-effective. However, when increasing the threshold to $500,000 per QALY, deflazacort had a 92% probability of being cost-effective. None of the large potential treatment effects modeled as rightward shifts in all the survival curves for eteplirsen indicated a potential for it to be cost-effective at the standard willingness-to-pay threshold of $150,000 per QALY (see Table ES6).

Table ES6. Primary Threshold Analyses Varying Treatment Effects of Eteplirsen as an Add-On Therapy to Prednisone and Supportive Care

Scenario	Treatment	Total Cost Difference	LY Difference	QALY Difference	Cost per QALY
10 Year Shift*	Eteplirsen	$12,670,000	5.15	4.70	$2,700,000
10 Year Shift Societal*	Eteplirsen	$12,820,000	5.15	4.70	$2,730,000
20 Year Shift*	Eteplirsen	$17,510,000	8.63	8.20	$2,140,000
20 Year Shift Societal*	Eteplirsen	$17,740,000	8.63	8.20	$2,170,000
40 Year Shift*	Eteplirsen	$24,010,000	12.95	12.42	$1,930,000
40 Year Shift Societal*	Eteplirsen	$24,350,000	12.95	12.42	$1,960,000

LY: life year, QALY: quality adjusted life year

*These involve parallel shifts in all the health state-related survival curves in the model.

Summary and Comment

Available evidence on the costs and utilities in health states associated with DMD were synthesized to allow estimation of the cost-effectiveness of deflazacort, as well as to consider threshold effects (QALYs required), for eteplirsen, given its current price. Specifically, deflazacort plus best supportive care were examined relative to prednisone plus best supportive care. In addition, eteplirsen and golodirsen were considered as add-on therapy to corticosteroids plus best supportive care. Since there was insufficient evidence of a treatment effect for eteplirsen, and no price or efficacy estimates for golodirsen, only threshold analyses for eteplirsen were reported.

For deflazacort, our base-case analyses showed incremental cost-utility ratios well above commonly accepted thresholds even with extremely favorable assumptions regarding treatment effects. The deterministic and probabilistic sensitivity analyses further supported this finding.

For eteplirsen, at its current price, threshold analyses suggested that it would not be cost-effective at commonly accepted thresholds even when assuming extremely favorable treatment effects that are not credible given current clinical evidence. Again, by extension, the same results would apply to golodirsen if it is priced similarly to eteplirsen.

The important limitations to consider are that current evidence on DMD only allowed for a five-health state model, and our assumption of upper bound (favorable), rather than exact treatment effects were modeled. While these are important to consider, the magnitude of the treatment costs relative to the potential health effects projected for DMD suggest serious concerns regarding the cost-effectiveness of these treatments at current prices. A broad set of threshold and scenario analyses suggest these concerns are robust to a wide set of potential variances in actual treatment effects and demonstrate that at current prices, the treatment effects would have to be substantially better than what the current available evidence reflects for these treatments to be cost-effective.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES7. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	N/A
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	Insurance coverage of deflazacort may make the drug more accessible to a wider population of DMD patients at lower cost.
This intervention will significantly reduce caregiver or broader family burden.	Greater delays in loss of muscle strength and ambulation from use of deflazacort compared with prednisone may reduce caregiver burden. Improvements in dystrophin levels from exon-skipping drugs, if shown to improve function, may also reduce caregiver burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	The exon-skipping drugs offer a novel mechanism of action that may benefit the subset of DMD patients whose mutations are amenable to skipping of exons 51 and 53.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Reduced caregiver burden may lead to greater ability of caregivers to continue working/return to work.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	As DMD is a progressive, fatal disease with no known cure, interventions that have the potential to restore dystrophin to levels of clinical significance may have impact on the natural history of the disease and disability caused by the disease. However, exon-skipping drugs have not yet been shown to yield clinical benefits.

Contextual Considerations

Table ES8. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	DMD is a progressive, fatal disease that results in substantial disability and decrement in quality and length of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Patients with DMD progress to needing high levels of assistance, particularly after loss of ambulation and as cardiac and respiratory muscles weaken.
This intervention is the first to offer any improvement for patients with this condition.	N/A
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Although exon-skipping drugs have not shown significant harms, small trials and limited follow-up time may lead to missing serious harms.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	It is uncertain whether increase in dystrophin levels caused by treatment with exon-skipping drugs is of clinical significance, and the lack of long-term studies limits conclusions about the durability of benefits with treatment of such drugs.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Standard outcome measures may not fully capture a patient's functional status, as many outcomes are effort dependent and do not measure the nuances of patient function (e.g., how easily does the patient accomplish a task or what compensatory mechanisms are being used?). Video evidence may give a more complete picture of functional status; however, these such outcomes have yet to be validated in a clinical trial setting.

Value-Based Price Benchmarks

We calculated the annual value-based price benchmarks (VBPBs) using cost per QALY and cost per LY gained thresholds for deflazacort for the treatment of DMD patients; these are presented in Table ES9. Given that the model assumed extremely favorable clinical assumptions for deflazacort (see Section 4 for further explanation), it should be noted that these VBPBs should be considered as the upper limit of the price ranges. VBPBs could not be calculated for eteplirsen or golodirsen in the absence of evidence demonstrating clinical benefits.

Table ES9. Value-Based Price Benchmark for Deflazacort Using Favorable Assumptions

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Per QALY Gained	$117,400	$19,900	$31,700	73% to 83%
Per LY Gained		$21,100	$33,500	71% to 82%

WAC: wholesale acquisition cost; QALY: quality-adjusted life year; LY: life year

*Price per year is for a 40 kg patient.

Potential Budget Impact

We used results from the cost-effectiveness model to estimate the potential budgetary impact of deflazacort in DMD patients aged five years and above. Because there was insufficient evidence to model the cost-effectiveness of eteplirsen and golodirsen, we did not estimate the budget impact of these treatments. To estimate deflazacort's potential budget impact, we first estimated the size of the DMD population eligible for treatment with deflazacort at approximately 6,200 patients over five years, or approximately 1,240 patients per year using published epidemiological evidence.[43]

Estimated annual per-patient budget impacts using deflazacort's list price ($117,400 per year), net price ($81,400 per year), and the threshold prices to reach $150,000, $100,000 and $50,000 per QALY ($31,700 per year, $19,900 per year, and $8,200 per year, respectively) compared to prednisone, annualized over five years, are presented below in table ES10. The annual per patient budget impact when using deflazacort relative to prednisone ranged from approximately $3,900 at its price to reach the $50,000 per QALY threshold to approximately $60,000 when using its WAC.

Table ES10. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per-Patient Budget Impact				
	At List Price	At Net Price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Deflazacort (Annualized Cost)	$83,200	$68,800	$38,900	$32,900	$26,800
Prednisone (Annualized Cost)	$22,900				
Deflazacort Budget Impact*	$60,300	$45,900	$16,000	$10,000	$3,900

QALY: quality-adjusted life year

*Difference between deflazacort and prednisone costs

The potential budget impact of treating the entire eligible population with deflazacort resulted in the total budget impact reaching only 23% of the ICER annual budget impact threshold ($819 million) if deflazacort was not discounted and priced at its WAC, or reaching only 18% of this threshold if deflazacort's net price was used. For the three cost-effectiveness threshold prices at $150,000, $100,000, and $50,000 per QALY, the potential budget impact reached only approximately 6%, 4% and 2% of the threshold, respectively.

1. Introduction

1.1 Background

Background

Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene (*DMD*) that result in progressive loss of muscle function, including skeletal and cardiac function. It is the most common pediatric muscular dystrophy with a prevalence of one in 3,500-5,000 live male births, or about 400 to 600 boys per year in the US.[44] Rarely, females who are carriers of a *DMD* mutation can also be symptomatic.[5]

DMD is caused by any of more than 2,000 mutations in the gene *DMD* that result in loss of expression of the dystrophin protein. The majority of patients (70%) have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing.[45] Dystrophin is expressed in skeletal and cardiac muscle, and in the brain; it forms an important part of the glycoprotein complex, strengthening and connecting muscle fibers. The absence or lack of functional dystrophin results in muscle degradation and scarring, leading to progressive skeletal weakness, wasting, and cardiomyopathy. Levels of dystrophin in patients with DMD are generally less than 3% of normal.[1] Severity of disease appears to vary with mutation, resulting in a heterogeneous population with differing rates of progression.[4,46]

Signs of DMD usually occur in early childhood, with a mean age of symptom onset of 2.5 years in affected children; however, diagnosis is often delayed until around age five due to the rarity of the disease.[47] Early symptoms include muscle weakness, frequent falls, inability to keep up with peers, difficulty with rising from a squatted position (Gower's sign), toe-walking, and difficulty going up and down the stairs. Untreated children with DMD usually progress to a loss of ambulation by age 10-12 years; treatment may delay this outcome.[6] Children may also have developmental delay and behavioral issues, as well as impaired growth, delayed puberty, and gastrointestinal complications (e.g., dysphagia and gastroparesis) from the loss of muscle contraction. Orthopedic complications such as contractures and scoliosis occur in most patients, typically after loss of ambulation. Bone health is a major long-term problem, as osteoporosis frequently occurs in later stages of the disease, with a high risk of fractures. Fatal respiratory or cardiac complications commonly develop in the second or third decade of life, with many deaths occurring in the setting of an acute infection such as pneumonia or after surgery.[7,8] However, treatment with corticosteroids and advanced supportive care such as assisted ventilation (non-invasive and invasive), spinal surgery, and prevention and management of cardiomyopathy-related heart failure have led to delays in disease progression and improved survival of patients with DMD such that some patients are now surviving into their 30s or 40s.[4,43] Medical costs of treating DMD are estimated at $22,500 annually and

increase substantially with disease progression due to increased health care utilization, particularly as patients lose the ability to walk and become non-ambulatory.[9-13]

DMD affects patient and caregiver quality of life in a variety of ways. Scores on health-related quality of life surveys for children with DMD are worse than those of healthy children and children with many other chronic illnesses, particularly for physical function.[48,49] Arm function, in particular, significantly influences quality of life.[50] Studies of DMD patients and caregivers have suggested that although physical quality of life declines with disease progression, scores on social functioning, mental health, and vitality may remain fairly stable throughout the disease course.[51] Though caregiver burden was high, most caregivers perceived those they cared for to be at least somewhat happy and in good to excellent health regardless of the patient's physical status.[48,52] Caregivers also tended to rate the patient's quality of life lower than the patient themselves.[53] Additionally, a review of quality of life studies suggests that there is not currently a standard instrument that is used across studies and that DMD patients and their caregivers have a complex quality of life profile that may not be fully captured by current standard tools.[53]

Treatment for DMD

Since DMD is a degenerative disease that affects multiple organ systems, care of DMD patients is provided by a multidisciplinary team, typically led by a neuromuscular specialist. Treatment for DMD includes supportive care and medications such as corticosteroids and exon-skipping therapies (Table 1.1).

Table 1.1. Treatments for DMD Evaluated in Report

Drug (Brand Name)	Manufacturer	US FDA Approval Date	Class of Drug	Method of Delivery	Approved Population
Deflazacort (Emflaza®)	PTC Therapeutics	February 2017	Corticosteroid	Oral	DMD patients 2 years and older
Eteplirsen (EXONDYS 51™)	Sarepta Therapeutics	September 2016	Exon-skipping of exon 51	Intravenous	DMD patients with mutations amenable to exon 51 skipping
Golodirsen	Sarepta Therapeutics	N/A	Exon-skipping of exon 53	Intravenous	N/A

DMD: Duchenne muscular dystrophy, N/A: not applicable, US FDA: United States Food and Drug Administration

Supportive Care

The natural history of DMD is such that patients have progressive muscle degeneration and weakness, leading to loss of function, which can be measured in a variety of ways, such as by ambulatory status[14] (see Table 1.2) or upper extremity strength (e.g., Brooke scale[54]). There is a risk of progressive contracture as the disease worsens, and thus physical and occupational therapy are

key interventions to maintain ambulation, minimize deformity, optimize respiratory function, and maintain skin integrity.[14] Additionally, patients may progress to needing assistive or mobility devices such as orthotics, power wheelchairs, and other adaptive equipment to maintain function. Home renovations and vehicle modifications may also be necessary in such situations, which may result in substantial out-of-pocket costs. Finally, as the respiratory muscles weaken, non-invasive ventilation may be necessary at first, and the use of invasive ventilation may be needed in later stages of the disease.

Table 1.2. DMD Stages of Disease[14]

Stage	Description
Stage 1: Presymptomatic	Shows no physical signs of disease Diagnosis may be suspected at this stage based on family history or elevated creatine kinase, and confirmed by genetic testing
Stage 2: Early Ambulatory	Displays Gowers' sign, waddling gait, toe walking Can climb stairs No respiratory, or cardiac compromise Rare orthopedic complications Diagnosis most commonly made in this stage
Stage 3: Late Ambulatory	Increasingly labored gait Losing ability to climb stairs and rise from floor May need orthopedic intervention for contractures Some risk of respiratory, cardiac compromise
Stage 4: Early Non-Ambulatory	May be able to self-propel Able to maintain posture May develop scoliosis and require surgical intervention Increasing risk for respiratory or cardiac compromise
Stage 5: Late Non-Ambulatory	Limited function of upper extremities Difficulty maintaining posture High likelihood of respiratory or cardiac compromise

Corticosteroids

Corticosteroids are a mainstay of therapy for DMD patients. They have been shown to improve muscle strength, prolong ambulation, delay the onset of scoliosis and reduce the need for surgery, preserve respiratory function, and delay onset of cardiomyopathy.[18,28,55,56] The exact mechanism of corticosteroids in DMD is unknown; anti-inflammatory and immunomodulatory effects are postulated, as well as potential repair of muscle fibers, regulation of the genes in muscle fibers, and alterations in cell signaling.[57,58]

In natural history studies of DMD, approximately two-thirds of patients with DMD were treated with steroids for at least one year, and up to 25 years.[24] The age and stage of disease at which to start steroid therapy is an individualized decision based on age, functional status, and pre-existing

risk factors for adverse effects, but such treatment is rarely started before age five.[14] Similarly, the length of treatment is also an individualized decision, and though there is a lack of consensus on steroid use during the non-ambulatory phase, some patients remain on steroids after loss of ambulation with goals of preserving upper limb strength and delaying progression of scoliosis, respiratory decline, and cardiomyopathy.[24,28,55,59,60] There is also a lack of consensus on the optimal dosing and dosing regimen to maximize benefits and minimize side effects – regimens of daily, weekly, weekend-only, and intermittent dosing (e.g., 10 days on/10-20 days off) of differing dosages have been used with no clear evidence on the superiority of one regimen.[61] An ongoing clinical trial comparing the efficacy of different corticosteroid regimens (daily prednisone vs. daily deflazacort vs. intermittent prednisone) may help address this question.[62]

Patients treated with long-term corticosteroid therapy are at risk for adverse events (AEs). Weight gain, Cushingoid appearance, hirsutism (unwanted hair growth), impacted linear growth, behavioral changes, fractures due to worsening osteoporosis, and cataracts have all been reported in patients taking corticosteroids, and may lead to discontinuation of therapy.[18,24] Lower doses and/or intermittent therapy may be associated with lower incidence of side effects.[18]

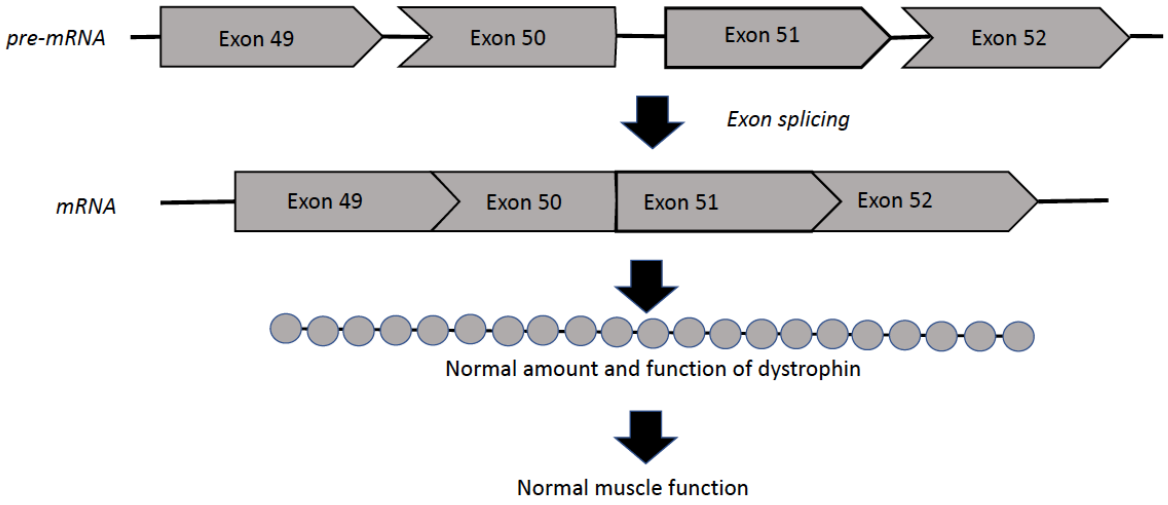
Corticosteroids, including prednisone, prednisolone, and deflazacort (Emflaza®, PTC Therapeutics), are most commonly used for treatment in DMD patients. While prednisone does not have a United States (US) Food and Drug Administration (FDA) indication specific for DMD, it is widely used for treating the disease. Prednisolone is the active metabolite of prednisone and is largely used outside of the US. For the purposes of this report, the term "prednisone" may refer to prednisone and/or prednisolone except where a specific corticosteroid or corticosteroid dosing is being discussed. Deflazacort is a glucocorticoid prodrug whose active metabolite acts on the glucocorticoid receptor to produce anti-inflammatory and immunosuppressant effects. It was first licensed for use overseas in the 1980s and was approved by the FDA with a specific indication for the treatment of DMD in February 2017. Due to differences in chemical structure from prednisone, deflazacort may have differential effects on calcium, sodium, and carbohydrate metabolism, as well as on the hypothalamic-pituitary-adrenal axis,[63] leading to possible differences in tolerability between the two drugs.

Exon-Skipping Therapies

As part of ribonucleic acid (RNA) synthesis, exons are connected to generate messenger RNA that encodes dystrophin (Figure 1.1a). In patients with DMD, mutations in the exons (regions that code for the dystrophin protein) of the *DMD* gene cause misalignments in the transcription reading frame that lead to nonfunctional or absent dystrophin (Figure 1.1b). Mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted (so-called "out-of-frame deletion"), leading to non-functional (and generally markedly shortened) protein being produced. The absence of functional dystrophin leads to inflammation and degeneration of muscle.

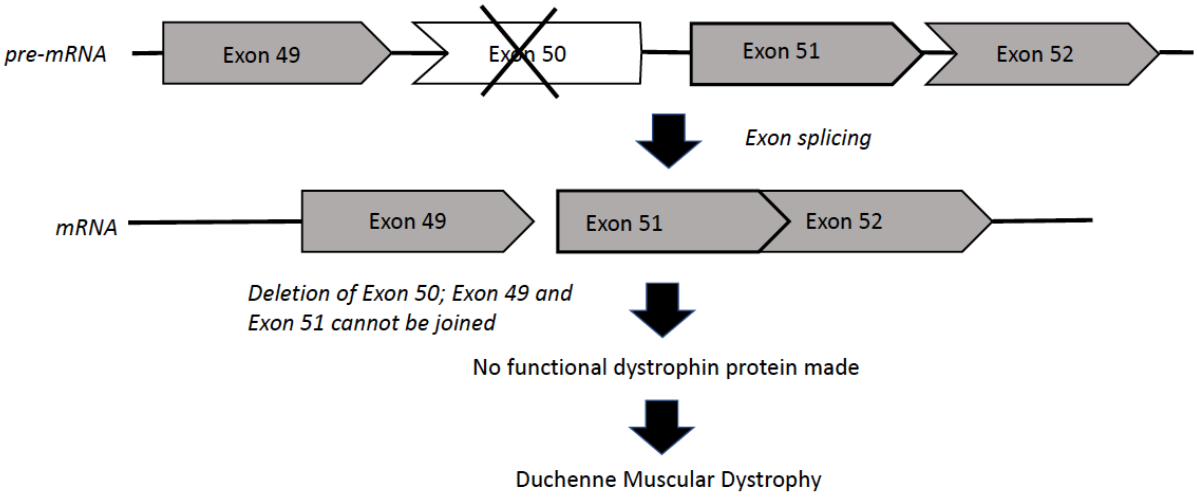
Exon-skipping therapies are anti-sense oligonucleotides that target dystrophin pre-messenger RNA (mRNA) and induce skipping of the mutated exons, converting the mutation into an in-frame mutation, and allowing downstream exons to be transcribed. The remaining exons form a shortened mRNA that encodes a shortened but partially functional dystrophin protein (Figure 1.1c). Animal models and observational data suggest that restoration of small amounts of dystrophin (between 2-4% of normal) may be beneficial in slowing progression of the disease,[15,16] though clinical correlation has yet to be established.

Figure 1.1a. Normal Synthesis of Dystrophin Protein



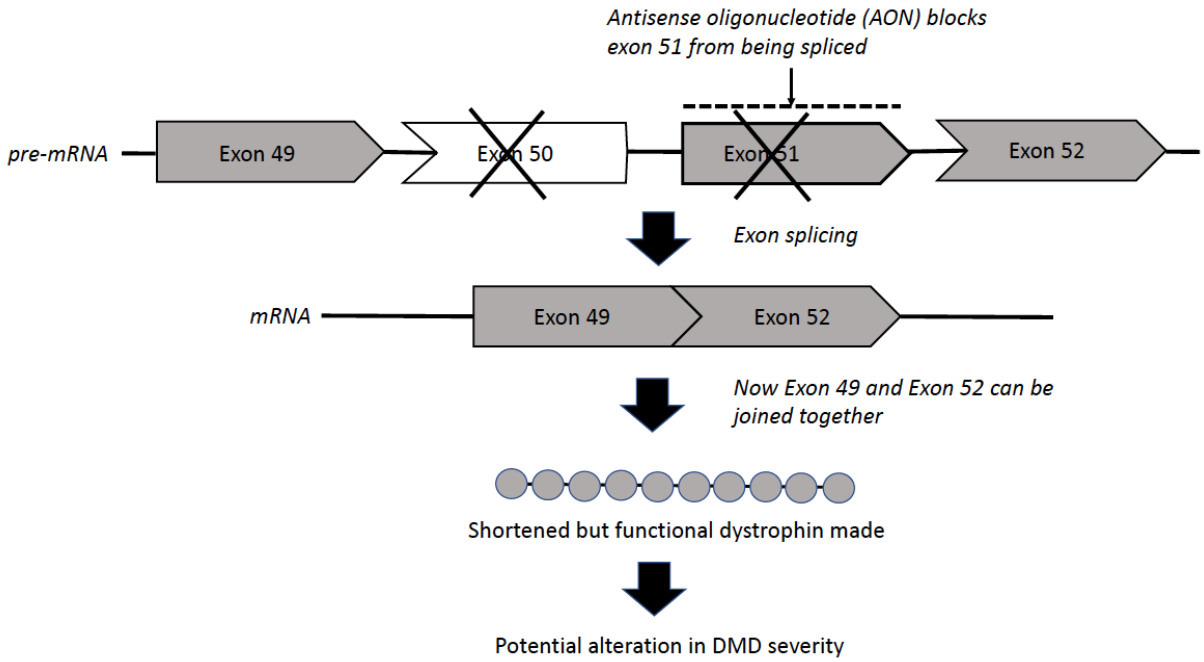
mRNA: messenger ribonucleic acid

Figure 1.1b. Exon Deletion Causing Lack of Dystrophin Production in DMD



mRNA: messenger ribonucleic acid

Figure 1.1c. Exon-Skipping Therapy Leading to Shortened but Functional Dystrophin Production



DMD: Duchenne muscular dystrophy, mRNA: messenger ribonucleic acid

Eteplirsen (EXONDYS 51™) was developed by Sarepta Therapeutics and was the first exon-skipping therapy for DMD to be approved by the FDA; it was approved in September 2016 for patients with mutations amenable to exon 51 skipping, which accounts for about 13% of the DMD population.[17] The FDA label states, "A clinical benefit of EXONDYS 51 has not been established." Eteplirsen is delivered through a weekly intravenous infusion and could potentially alter the DMD disease course through increasing the production of functional dystrophin in patients taking the drug.

Golodirsen (SRP-4053) is a new exon-skipping therapy developed by Sarepta Therapeutics for patients with mutations amenable to exon 53 skipping, estimated to be 9% of the DMD population.[17] Golodirsen is delivered through a weekly infusion. Based on promising results from a Phase I/II trial[64], golodirsen is under evaluation for accelerated approval by the FDA, with an expected decision date in August 2019. A Phase III trial (NCT02500381) is ongoing.

Future Therapies

There are other treatment targets in DMD patients that are being pursued, including therapies to target muscle degeneration and fibrosis, inhibit myostatin, reduce inflammation, bypass aberrant stop-codons, and modulate the protein utrophin (a protein similar to dystrophin that may be able to replicate some of dystrophin's functions).[65] There are also additional exon-skipping therapies targeting specific mutations under development, including casimersen (exon 45 skipping drug),

which has shown promise in an early trial.[66] Gene replacement therapy is under investigation, with several active human clinical trials. Finally, gene editing techniques such as CRISPR/Cas9 may be useful in treating DMD in the future; however, numerous scientific and ethical issues surrounding gene editing will need to be resolved before human clinical trials can take place. Such therapies may be used to augment or replace current therapies to improve function and survival for DMD patients.

1.2 Scope of the Assessment

Although new and promising treatments for DMD are emerging, questions remain regarding the indications, timing, safety, acceptability, and how well the costs of drug treatment for DMD align with potential patient benefits. This project evaluates the health and economic outcomes of deflazacort, eteplirsen, and golodirsen for patients with DMD. We assessed these three treatments under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because the assessment meets the following criteria:

- The eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.[67,68]
- There are no ongoing or planned clinical trials of the treatments for a patient population greater than approximately 10,000 individuals.

Based on population studies, the prevalence of DMD in the US is estimated to be 0.4 per 10,000 males, resulting in approximately 6,000 affected people in the US.[43] The ICER value framework for ultra-rare conditions includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

The scope for this assessment is described on the following pages using the Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) framework. Evidence was abstracted from randomized controlled trials (RCTs) and nonrandomized studies as well as high-quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon AEs. Our evidence review includes input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence was summarized qualitatively or quantitatively. We sought out head-to-head studies of the interventions and comparators of interest. We also considered combined use of direct and indirect evidence in network meta-analyses (NMA) of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis were provided in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Research Questions

The following research questions were developed with input from clinical experts, patients, and patient groups:

1. In all patients with DMD, what is the comparative efficacy, safety, and effectiveness of deflazacort versus prednisone?
2. In patients with a mutation of the *DMD* gene amenable to exon 51 skipping, what is the comparative efficacy, safety, and effectiveness of eteplirsen versus supportive care and corticosteroids alone?
3. In patients with a mutation of the *DMD* gene amenable to exon 53 skipping, what is the comparative efficacy, safety, and effectiveness of golodirsen versus supportive care and corticosteroids alone?

PICOTS Criteria

Populations

Our review focuses on three populations, defined as follows:

1. All individuals with DMD. We reviewed evidence on the corticosteroid deflazacort in this population based on the FDA-approved indication.
2. All individuals with a mutation of the *DMD* gene amenable to exon 51 skipping. We reviewed evidence on eteplirsen in this population based on the drug's mechanism of action and FDA-approved indication for eteplirsen.
3. All individuals with a mutation of the *DMD* gene amenable to exon 53 skipping. We reviewed evidence on golodirsen based on the mechanism of action and clinical trial population.

Interventions and Comparators

The list of interventions was developed with input from patient organizations, researchers, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

1. For individuals who are candidates for deflazacort, we compared deflazacort to prednisone.
2. For individuals who are candidates for eteplirsen, we compared eteplirsen plus background corticosteroids (i.e., those used per standard care guidelines) to supportive care with corticosteroids alone.
3. For individuals who are candidates for golodirsen, we compared golodirsen plus background corticosteroids to supportive care with corticosteroids alone.

Outcomes

We sought information on a mix of clinical and patient-centered outcomes, as well as safety data.

The key outcomes of interest are:

- Mortality
- Mobility
- Cardiac issues (e.g., cardiomyopathy, arrythmias, and heart failure)
- Respiratory complications (e.g., dyspnea, respiratory failure, hospitalization due to pneumonia or atelectasis, respiratory-induced cardiac arrythmias)
- Bone health (osteoporosis, fractures, and sequelae of fractures such as fat embolism)
- Health-related quality of life
- Activities of daily living
- Caregiver burden (e.g., parent employment, home caregiving)
- Education and employment-related outcomes (e.g., ability to attend work or school)

Intermediate and surrogate outcomes of interest include:

- Dystrophin production
- Motor function
- Respiratory function
- Cardiac function
- Spinal curvature
- Bone mineral density

Safety outcomes of interest include:

- AEs and SAEs
- SAEs leading to discontinuation of drug
- Deaths

Additional safety outcomes of interest specific to corticosteroids include:

- Weight gain
- Decreased linear growth
- Cataracts
- Neurodevelopmental and behavioral issues
- Hirsutism
- Other complications of chronic corticosteroid therapy

Timing

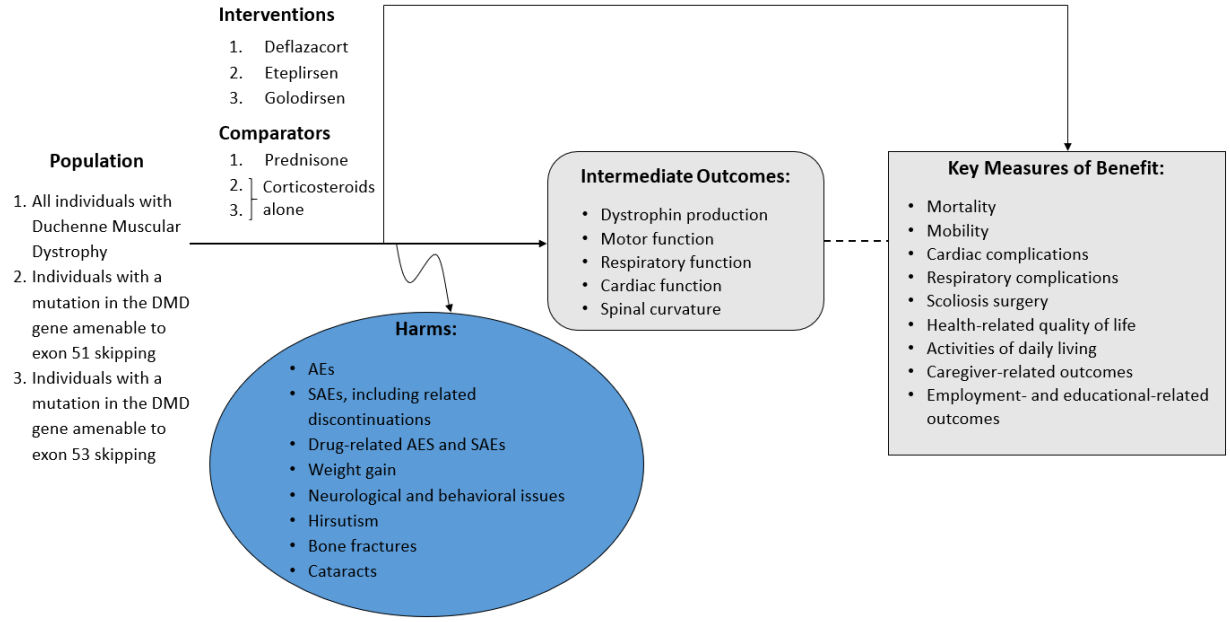
Evidence on intervention effectiveness and harms were derived from studies of any follow-up duration. However, for studies assessing longer term complications of steroids such as cataracts, we will only consider studies with a duration of at least six months.

Setting

All relevant settings were considered, including inpatient, outpatient/clinic, office, and home settings.

Analytic Framework

Figure 1.2. Analytic Framework



AE: adverse event, DMD: Duchenne muscular dystrophy, SAE: serious adverse event

The analytic framework for this review is shown in Figure 1.2. The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded box are intermediate outcomes (e.g., dystrophin production), and those within the squared-off box are key measures of benefit (e.g., mobility). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the AEs of treatment which are listed within the blue ellipse.[69]

1.3 Definitions

4-stair climb: The time needed to climb a standard set of four stairs, with or without handrails, measured in seconds. In DMD patients, it can be used as a marker of disease progression.

10-meter walk/run: A measure of how fast a patient can walk in meters per second. The patient is timed with a stopwatch for six meters, allowing for two meters on each side for acceleration and deceleration. Has been used as an outcome measure in patients with DMD. A time of greater than 12 seconds is associated with loss of ambulation within the next 12 months in DMD patients; conversely a time of six seconds or less is predictive of continued ambulation.[70] Some studies also use 30 feet for the distance for the timed test rather than 10 meters.

Dystrophin: Dystrophin is a protein found in muscle cells. It helps strengthen muscle fibers and protect them from breaking down as they contract and relax. Deficiency in dystrophin leads to muscle breakdown and loss of function and is the main defect in DMD.

Forced vital capacity (FVC): A measure of the total amount of air expelled from the lungs during a test to measure lung function. In patients with DMD, the test is used to follow lung function and significant reduction in FVC can predict the need for assistive ventilation.[70]

Motor Function Tests: A series of tests to assess motor function in patients with DMD. The tests included in trial outcomes vary from trial to trial, but often include tests for gait such as the 10-meter walk/run, 4-stair climb, rising from supine or sitting on the floor to standing, running/walking for 30 feet, and propelling a wheelchair for 30 feet.

Medical Research Council (MRC) Scale for Muscle Strength: A standardized assessment of muscle power used to assess strength in DMD patients. Muscle strength is measured on a 0-5 scale, with 0 indicating no movement in the muscle and 5 indicating full strength.

6-Minute Walk Test (6MWT) (also may be called six-minute walk distance [6MWD]): A measure of how far a patient can walk in six minutes on a hard, flat surface. It is considered predictive of

disease progression in muscular dystrophy patients over the age of one, and in DMD, the ability to walk distances greater than 325 meters during the test has been linked to slower disease progression.[71]

1.4 Insights Gained from Discussions with Patients and Patient Groups

As part of our scoping process, we reached out to patient groups, including advocacy and research groups, as well as individual parents and caregivers to gain insight into important topics for discussion in the DMD community. Additionally, three patient groups, six parents/caregivers, and one patient advocate submitted comments during the Open Input Period and the Public Comment Period on the Draft Scoping Document. These comments shape the discussion below.

Caregivers (most commonly parents) described the physical, financial, and emotional tolls of caring for children with DMD, from receiving the life-changing diagnosis to trying to maximize daily life and function as the disease progressed. Caregivers and patient groups highlighted several concerns related to caring for DMD patients. Access and cost of treatment were of major concern, particularly with exon-skipping therapies. Additionally, prior to approval in the US, deflazacort was available to be imported for approximately $1,000 (US dollars) per year. Although many insurers are now covering deflazacort after its approval, leading to potentially increased access and decreased financial burden, insurers often require prior authorization and/or demonstration of failure of prednisone, which creates an additional barrier for patients to obtain the medication.

Financial burdens outside of medical costs that are not covered by insurance (e.g., obtaining wheelchair-accessible transportation, costs of renovations to make homes accessible, travel costs to access specialty care) were often mentioned by caregivers/parents as a major concern. Many caregivers reported spending significant amounts of time navigating the insurance system, for both treatment approval and to obtain equipment such as wheelchairs, and worried that there could be significant financial and health consequences due to insurance-related delays.

The high caregiving burden for patients with DMD was often mentioned, including the anxiety, depression, and isolation that can result from caring for a child (or children) with a severe illness. Caregiver burden was mentioned to increase when children lost the ability to ambulate and also when upper extremity mobility was lost, as these events represent the loss of independence for patients, resulting in the need for more assistance from caregivers. Thus, delaying loss of ambulation and upper extremity function for as long as possible was mentioned as important patient-centered outcomes. Additionally, weight gain was cited as an important side effect for patients with DMD treated with corticosteroids, as excessive weight gain could lead to both physical and psychological harm for DMD patients, including greater difficulty with ambulation, increased risk of fractures, increased difficulty for caregivers to lift and transfer patients, and impaired sense of well-being.

Caregivers and patient groups expressed concern that research studies did not include broad enough populations, given the heterogeneity of the DMD population, and that a lack of natural history data impaired the community's ability to accurately assess the effects of interventions. They also cited a lack of validated outcome measures in clinical trials that adequately reflect function in the context of daily life activities (e.g., outcome measures that assess muscle strength in the context of daily life activities, not just on standardized tests), and that lack of such measures may lead to an underestimation of a drug's benefit, as maintenance of activities of daily living may be an important indicator of independence. Furthermore, "improvement" should also include stabilization and/or slowed decline, as preservation of function and independence are of great importance to patients and their caregivers. Patient groups suggested that non-traditional sources of data, such as videos, may be important in capturing and more accurately assessing the full spectrum of treatment benefit, and that validation of video data should be encouraged. Video data are further discussed in Controversies and Uncertainties in Section 3.

Additionally, while they hoped that new breakthrough treatments would help improve quality of life for patients with DMD, particularly by improving or stabilizing functional status and independence, parents were also concerned about the potential side effects, durability, and high cost of such therapies.

1.5 Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invited manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. For this report, no manufacturer submitted information on development of production costs that they believed would be an important factor in justifying the price of their product.

1.6 Potential Cost-Saving Measures in DMD

ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for DMD (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of DMD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with DMD that could be reduced, eliminated, or made more efficient. No suggestions were received.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for its US commercial health plans' coverage policies for eteplirsen, current as of December 2018.[72] Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data on 240 specialty drugs, 200+ diseases, and 8,800 decisions from the following 17 largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC). We manually searched the same payers for policies related to deflazacort, which is not currently included in the SPEC database. We also reviewed publicly available coverage policies from MassHealth and Husky Health Connecticut. We searched for National or Local Coverage Determinations (NCDs or LCDs) from the Centers for Medicare and Medicaid Services (CMS), and were unable to locate any such policies for deflazacort or eteplirsen. At the time this report was published, the FDA had yet to issue a decision on golodirsen, precluding a survey of its coverage policies.

Deflazacort

For deflazacort, out of the 17 surveyed commercial payers, four payers (24%; BCBSNJ, BCBSTN, HCSC, Highmark) did not have publicly available coverage policies, two payers (12%; Aetna and Humana) did not cover deflazacort, and 11 payers (65%) covered deflazacort for patients who have experienced a failure, contraindication, or intolerance to prednisone.[73-83] Of the payers who covered deflazacort, UHC, BCBSFL, BCBSNC, and BCBSMA defined a trial period of at least six months on prednisone prior to approval for deflazacort.[74,76,81,84] Emblem, Cigna, CareFirst, BCBSFL, BCBSNC, and IndepBC required patients to be five years of age or older.[74,76,77,79,82,83] BCBSNC's initial authorization covers deflazacort for three months; BCBSFL, Centene, and Anthem for six months; and all other payers authorized treatment for 12 months.[73,74,76,78] CareFirst, Cigna, BCBSNC, Centene, and IndepBC all specified that continued authorization would be dependent on documentation of positive clinical response, while the latter two additionally specified that the dose prescribed not exceed 0.9 mg/kg/day.[76-79,83] Five payers (30%) also placed provider subgroup restrictions; BCBSNC, Centene, and IndepBC required the prescribing physician to be a neurologist, BCBSMI required a physician specialized in DMD, and BCBSFL required the patient be evaluated by

an ophthalmologist for deflazacort-related AEs such as cataracts, in order to obtain continued authorization.[74-76,78,79]

MassHealth's general fee-for-service authorization criteria for deflazacort were comparable to that of commercial payers.[85] MassHealth required patients to be at least five years of age, have experienced significant weight gain which was not lessened by 25% dose reduction during a trial of prednisone, have a neuromuscular neurologist who prescribes or provides consult notes for treatment, and be receiving an appropriate weight-based dose of 0.9 mg/kg/day.[85] Continued authorization required documentation meeting initial criteria for age, provider, and appropriate dose for weight.[85] We were unable to find a coverage decision for deflazacort from Husky Health Connecticut.

Eteplirsen

Of the 17 surveyed commercial payers, 16 (94%) issued a utilization management policy for eteplirsen, nine payers (53%) covered the treatment (Aetna, Anthem, BCBSMA, BCBSTN, CareFirst, Cigna, Emblem, Humana, and UHC), and seven payers (41%) did not cover it.[72] IndepBC was the only surveyed payer that did not have a publicly-available coverage policy.[72] Payers who did not provide coverage (BCBSFL, BCBSMI, BCBSNC, BCBSNJ, Centene, HCSC, and Highmark) considered eteplirsen to be investigational with insufficient evidence to support its clinical benefit for DMD.[72]

Of the nine commercial payers who covered eteplirsen, eight payers (89%) applied coverage criteria that were more restrictive than the FDA label, while CareFirst's policy was equivalent (Table 2.1).[72] Patient subgroup coverage criteria were applied to patient age, and requirements for patient ambulation and concurrent corticosteroid therapy. When specified, restrictions for patient age fell between a range of seven to 14 years.[72] Criteria for ambulation were either derived from a 6MWT measure ranging from at least 180-300 meters or stated as a patient achieving ambulation without assistance or retaining meaningful voluntary motor function (e.g., able to speak or manipulate objects using upper extremities).[86] CareFirst was the only payer to not place any criteria for ambulation for approval.[72] Emblem was the only payer to apply a step therapy protocol requiring the patient to first have an intolerable AE resulting from at least 24 weeks of corticosteroid therapy or an adequate trial of deflazacort prior to approval for eteplirsen.[72] Four payers (44%) applied provider subgroup restrictions that varied by payer (Table 2.1).[72]

Continued authorization requirements varied between commercial payers. Except for CareFirst, all payers required patients to remain independently ambulatory; UHC additionally required achieving at least 300 meters on the 6MWT; and BCBSTN and Cigna both required documentation of positive clinical response.[72]

Both public payers, MassHealth and Husky Health Connecticut, required prior authorization for coverage of eteplirsen for DMD, and placed restrictions on ambulatory ability, prior corticosteroid

therapy, and type of provider (Table 2.1).[87,88] MassHealth additionally required that the member have timed function test measurements for a timed ten-meter walk/run, timed floor to stand, timed four-step descend, and timed sit to stand.[88] Continuing authorization criteria for MassHealth included stable or improved 6MWT, appropriate dosing, continuation of or contraindication to corticosteroids, and stable or improved response to at least two of the measured timed function tests.[88] Husky Health Connecticut required patients to be ambulatory without assistance and achieve at least 180 meters on the 6MWT for continued authorization.[87]

Table 2.1. Private and Public Coverage Policies for Payers Who Cover Eteplirsen for DMD

Coverage Criteria	Aetna[89]	Anthem[90]	BCBSMA[91]	BCBSTN[92]	CareFirst[86]	Cigna[93]	Emblem[94]	Humana[95]	United Healthcare[84]	MassHealth – Tufts Health Plan*[88]	Husky Health Connecticut*[87]
Age	<14 years	NS	≥7 years	NS	NS	NS	NS	NS	NS	NS	NS
6MWT/ Ambulatory Criteria	≥180 meter	Ambulatory without assistance	Ambulatory without assistance	Voluntary motor function is maintained	NS	≥200 meter	≥300 meter	Ambulatory without assistance	≥300 meter	≥200 meter	≥180 meter
Corticosteroid Therapy	NS	NS	Must be concurrently receiving corticosteroid therapy	At least 6 months on corticosteroids prior to initiation of eteplirsen	NS	NS	Must be concurrently receiving corticosteroid therapy	NS	NS	At least 6 months on corticosteroids prior to initiation of eteplirsen or contraindication to corticosteroid	At least 6 months on corticosteroids prior to initiation of eteplirsen
Provider Therapy Restrictions	Physician specialized in treatment of DMD	NS	Board certified or board eligible neurologist	NS	NS	NS	Pediatric neurologist specialized in DMD	NS	Neurologist with expertise in DMD	Neuromuscular neurologist	Physician specialized in treatment of DMD
Step Therapy Protocol	No	No	No	No	No	No	Yes	No	No	No	No
Initial Authorization	NS	12 months	6 months	6 months	Indefinite authorization	6 months	4 weeks	NS	8 weeks	NS	6 months

6MWT: 6-Minute Walk Test, BCBSMA: Blue Cross Blue Shield of Massachusetts, BCBSTN: Blue Cross Blue Shield of Tennessee, DMD: Duchenne muscular dystrophy, NS: not specified

*Public payer.

Payers who do not cover eteplirsen for DMD: Blue Cross Blue Shield of Florida, Blue Cross Blue Shield of Michigan, Blue Cross Blue Shield of North Carolina, Blue Cross Blue Shield of New Jersey, Centene, HCSC, and Highmark.

2.2 Clinical Guidelines

American Academy of Neurology (AAN)

Practice Guideline Update Summary: Corticosteroid Treatment of DMD, 2016[96]

The AAN recommends either prednisone or deflazacort as a corticosteroid intervention for children with DMD. The guidelines cite evidence that prednisone improves strength and pulmonary function, and likely improves timed motor function, reduces the need for scoliosis surgery, and delays cardiomyopathy onset. The optimal dose for prednisone is stated to be 0.75 mg/kg/day; 10 mg/kg/weekend is equally effective over a 12-month duration although long-term effects are currently unknown. No recommendation for a maximum dose was given. If significant AEs develop, dose strength can be reduced to 0.3 mg/kg/day, although efficacy may be diminished. Deflazacort has also been shown to improve strength and timed motor function tests, and delays loss of ambulation by up to 2.5 years. In addition to offering similar benefits as prednisone for cardiac and respiratory outcomes, there is observational evidence that deflazacort may extend survival after five to 15 years of follow up. When compared to each other, prednisone may be associated with greater weight gain during first year of treatment while deflazacort may increase risk of cataracts. The daily preferred dosing regimen for prednisone was also associated with significant risk of weight gain, hirsutism, and Cushingoid appearance. There were insufficient data to make any conclusions or recommendations on the benefit of prednisone for survival, an optimal dose for deflazacort, or an effect of corticosteroid therapy on quality of life. The AAN suggests that patients and their families receive counseling regarding the variable evidence, availability, cost, and AE profiles of corticosteroid treatment prior to deciding between prednisone and deflazacort.

Centers for Disease Control and Prevention (CDC)

Duchenne Muscular Dystrophy Care Considerations, 2018[45,97,98]

Developed in collaboration with: TREAT-NMD Network, Muscular Dystrophy Association (MDA), and Parent Project Muscular Dystrophy (PPMD)

The Duchenne Muscular Dystrophy Care Considerations are a CDC-funded effort to summarize three articles published in *Lancet Neurology* and provide guidance for DMD management with an emphasis on multidisciplinary care and patient quality of life. The Care Considerations steering committee recommends initiating corticosteroid treatment with either prednisone or deflazacort, ideally during the ambulatory stage prior to significant physical decline. Initiation of treatment is recommended after a nutrition consultation and a discussion of potential side-effects. Steroid management is encouraged to help maintain muscle strength and function, lengthen time in ambulation, preserve upper limb and respiratory function, and reduce need for scoliosis surgery.

When ambulatory, the recommended starting dose for prednisone is 0.75 mg/kg/day and for deflazacort is 0.9 mg/kg/day; continued steroid use is recommended in the non-ambulatory stage. For management of side-effects, steroid treatment is not to be stopped abruptly but rather the dosage may be reduced by 25-33% if side-effects are intolerable, followed by a reassessment after one month. The committee notes that deflazacort may increase risk of growth delay and cataracts, however, it may lower risk of weight gain and behavioral problems when compared to prednisone. The choice of which steroid to initiate can depend on family and specialist's preference, availability in country of residence, cost, and perceived side effects. The committee acknowledges other drugs approved for mutation-specific types of DMD (e.g., eteplirsen approved in the US, ataluren approved in several European Union countries), however, the committee provides no guidance on their use given the current paucity of evidence.

National Institute for Health and Care Excellence (NICE)

Eteplirsen for Treating Duchenne Muscular Dystrophy (ID: 1003), 2018[99]

The Committee for Medicinal Products for Human Use—part of the European Medicines Agency—concluded that the available evidence for eteplirsen did not satisfactorily demonstrate a treatment effect and therefore advised against approval of eteplirsen for DMD management. Consequently, NICE suspended its evaluation of eteplirsen in July of 2018. There was no available guidance provided by NICE regarding deflazacort for treatment of DMD.

3. Comparative Clinical Effectiveness

3.1 Overview

Our review of the clinical effectiveness of deflazacort in comparison to prednisone and the exon-skipping therapies (eteplirsen and golodirsen), each in comparison to supportive care and corticosteroids alone, was informed by the evidence from available clinical studies meeting the PICOTS inclusion criteria, whether in published or unpublished form (e.g., conference abstracts or presentations, and FDA review documents). The scope of the review is detailed in Section 1.2.

We focused on reviewing the evidence on clinical benefits, as well as potential harms of deflazacort versus prednisone for all DMD patients, eteplirsen versus supportive care and corticosteroids alone for patients with a mutation of the *DMD* gene amenable to exon 51 skipping, and golodirsen versus supportive care and corticosteroids alone for patients with a mutation of the *DMD* gene amenable to exon 53 skipping. We sought evidence on the outcomes described in Section 1.2.

As discussed in ICER's Value Assessment Framework Modifications for Ultra-Rare Diseases, there are important challenges to generating high quality evidence for emerging treatments of ultra-rare diseases. Randomized trials may be difficult, and comparisons with historical controls and the use of surrogate outcomes may be necessary.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on deflazacort, eteplirsen, and golodirsen for DMD followed established best methods.[100,101] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[102] The PRISMA guidelines include a list of 27 checklist items, which are listed in Appendix Table A1. This review was registered with PROSPERO (CRD42019127727) and the full research protocol is available online (https://osf.io/mqh75/).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included full-text articles as well as abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the PICOTS elements described in Section 1.2. The search strategies

included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are available in Appendix Tables A2-A3.

To supplement the database searches, we performed manual checks of the reference lists of included trials and reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Studies meeting the PICOTS criteria described in Section 1.2 were eligible for our review. To be included, studies were required to assess deflazacort, eteplirsen, or golodirsen in patients with DMD. For any study that assessed supportive care, we accepted and used the study's definition of supportive care. We excluded studies assessing only supportive care (e.g., comparative studies of different supportive care options or single-arm supportive care studies), and studies assessing corticosteroids with unstratified results of deflazacort and prednisone.

Data Extraction and Quality Assessment

Data from included studies were extracted directly into Microsoft Excel. Data elements extracted include a description of patient populations (extent of ambulation, motor function at baseline, age at treatment initiation), sample size, duration of follow-up, funding source, study design features (randomization, location), interventions (agent, dosage, frequency, routes of administration), concomitant therapy allowed and used (e.g., any pharmacological or non-pharmacological agent along with frequency and schedules), outcome assessments, results, and quality assessment for each study.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[103]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We assessed publication bias for deflazacort, eteplirsen, and golodirsen using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. We considered any such studies to indicate the presence of publication bias. We did not

find evidence of any study completed more than two years ago for any of the drugs that has not subsequently been published.

Data Synthesis and Statistical Analyses

For each outcome of interest, the results of the studies are presented in text or tables. When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. We recognize the difficulty in validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. As such, we aim to add specific context to our findings regarding potential challenges in study design, when possible.

Data on relevant outcomes were summarized in evidence tables (see Appendix D) and are described in the text below. Due to major differences in entry criteria, patient populations, outcome assessments, and the lack of available patient-level data in the trials of deflazacort and the exon-skipping therapies, we could not quantitatively synthesize the trial data with a meta-analysis or NMA. Instead, we focused our attention on describing the comparisons made within the clinical trials of each agent.

3.3 Results

Study Selection

Our literature search identified 1,096 potentially relevant references (see Appendix Figure A1), of which 26 references (14 publications and 12 conference abstracts) related to eight randomized controlled trials (RCTs) and nine observational studies met our inclusion criteria. Primary reasons for study exclusion included study population outside of our scope (e.g., patients with Becker Muscular Dystrophy [BMD]), interventions not of interest (e.g., ataluren), comparators not of interest (e.g. healthy population, different disease), outcome reporting (e.g., irrelevant to scope or unstratified between the corticosteroids), and study type (e.g., case series). Details of all included studies are summarized below and in Appendix D.

Corticosteroids (Deflazacort vs. Prednisone)

A total of 10 references relating to three RCTs[19-21] and seven observational studies[22-28] comparing deflazacort to prednisone met our inclusion criteria.

Exon-Skipping Therapies (Eteplirsen and Golodirsen)

We included five references (three publications and two conference abstracts) relating to one Phase IIb RCT (Study 201), one open-label extension (Study 202), one single-arm study (Study 204),

and one ongoing Phase III study (Study 301) of eteplirsen.[29,31,33,104,105] In addition, we identified the FDA advisory committee briefing material on eteplirsen.[34]

For golodirsen, only one reference (conference abstract) relating to a Phase I/II RCT was identified.[32]

Quality of Individual Studies

We rated the quality of all three RCTs for deflazacort versus prednisone (Griggs 2016 was rated as good quality, Bonifati 2000 was rated as fair quality, Karimzadeh 2012 was rated as poor quality), as well as one Phase IIb RCT for eteplirsen (Study 201 was rated as fair quality) using the United States Preventive Services Task Force (USPSTF) criteria. The criteria included details regarding the comparability of the groups, investigator/patient blinding, intervention definitions, outcome definitions, and validity of outcome assessments (e.g., missing data). For trials to be categorized as fair, they were missing one or two of these USPSTF criteria. The one poor trial did not have comparable groups, non-differential loss to follow-up, and participant blinding.

The other trials were non-comparative or observational in trial design or unpublished RCTs (e.g., Phase III RCT of eteplirsen & Phase I/II RCT of golodirsen). Consequently, we did not assign quality rating to these trials. Instead we highlight limitations, uncertainties, and gaps in the evidence in these trials in the Controversies and Uncertainties section.

Corticosteroids

Evidence comparing deflazacort and prednisone is somewhat limited by potential selective reporting and few high-quality trials. It is possible that motor outcomes including time to loss of ambulation may be better with deflazacort, but results were inconsistent across and within trials, and this is uncertain. Undesired weight gain appears to be greater with prednisone than deflazacort, while cataract formation and reduction in growth appear to be greater with deflazacort. Evidence on other important harms is inadequate to come to definite conclusions and overall does not appear to clearly favor either deflazacort or prednisone.

Overview of Trials

RCTs

As noted above, we identified three RCTs comparing deflazacort and prednisone (Griggs 2016, Karimzadeh 2012, and Bonifati 2000).[19-21]

Griggs 2016 was a 52-week, multicenter, Phase III, double-blinded (Investigators and patients) RCT that compared the safety and efficacy of deflazacort, prednisone, and placebo in 196 boys (aged 5-

15 years) diagnosed with DMD. The trial was originally conducted in the US and Canada in 1995 but not published until 2016.[19] As the distinction between DMD and BMD was less clear at the time of the study, approximately 4% (7/196) of patients enrolled would today be classified as having BMD. The trial consisted of two parts; in part one, patients were randomized to three active treatment arms of either deflazacort 0.9 mg/kg/day (n=51), deflazacort 1.2 mg/kg/day (n=49), prednisone 0.75 mg/kg/day (n=46), or placebo (n=50) for 12 weeks. Randomization was stratified by center and ambulatory status of patients (ambulatory vs. non-ambulatory). In part two, placebo-treated patients were re-randomized to one of the three active treatment groups and all patients were followed for an additional 40 weeks. Although two different doses of deflazacort were evaluated in this study, we summarize only the findings relevant to the FDA approved dose (deflazacort 0.9 mg/kg/day). The primary clinical outcome evaluated in Griggs 2016 was the change in average muscle strength from baseline to week 12, as assessed by the modified MRC scale.[19] Secondary efficacy endpoints included change in average muscle strength from week 12 to week 52 and changes in pulmonary function from week 12 to week 52. Timed functional testing (standing from lying position, climbing four stairs, walking/running 30 feet, and propelling a wheelchair 30 feet) was included as an additional endpoint. Safety was assessed by vital signs (including height, weight, and body mass index [BMI]), the incidence of AEs, and changes in physical examinations or clinical laboratory findings.[19]

Karimzadeh 2012 was a single-blinded (patient only) RCT conducted in Iran.[20] Thirty-four boys (aged 3-10 years) diagnosed with DMD were randomized to either deflazacort 0.9 mg/kg/day (n=17) or prednisone 0.75 mg/kg/day (n=17) for a period of 18 months. Eight of the enrolled patients (three from the deflazacort group and five from the prednisone group) were excluded shortly after the trial commenced mainly due to lack of follow-through with study procedures. In addition, four patients in the prednisone group discontinued treatment after 12 months due to uncontrolled weight gain and were excluded from the analysis. The main clinical outcome was the mean change in motor function at 12 and 18 months.[20] Measurements of motor function comprised of three assessments: four-stair climb, rising from chair and floor, and walking 10 meters (32 feet) on flat ground. Functional scores were reported as a composite score that included all three assessments, each rated on a three-point scale. An increase in scores indicated worsening of muscle function, while a decrease indicated improvement. Pulmonary assessments were conducted annually. Safety was evaluated by measuring changes in weight and height percentiles for both treatment groups at 12 and 18 months.[20]

Bonifati 2000 was a 52-week double-blinded (investigators and patients) RCT of 18 boys (aged 5-15 years) diagnosed with DMD that was conducted at two neuromuscular centers in Italy.[21] Patients were randomized to either deflazacort 0.9 mg/kg/day (n=10) or prednisone 0.75 mg/kg/d (n=8). Randomization was stratified based on age and disease severity. Seven ambulatory boys with DMD served as a natural history control group. The efficacy outcomes assessed were change in muscle

strength, as evaluated by the MRC scale, and a functional assessment composed of the four-stair climb, rise from sitting position, and walking 10 meters on flat ground.[21] Higher functional scores indicated lower levels in motor function. Motor function was reported as a composite score; results of the individual functional assessments were not reported. Safety was evaluated by means of body weight measurements, biochemical and neurological tests, as well as side effects reported by the parents.[21]

Key baseline characteristics of the populations enrolled in the three RCTs are presented in Table 3.1.

Table 3.1. Baseline Characteristics of RCTs Comparing Deflazacort to Prednisone

Study	Arm	N	Mean Age, Years	Mean Height, cm	Mean Weight, kg	Mean BMI
Griggs 2016[106]	Deflazacort 0.9 mg/kg/day	51	8.8	131.0	31.0	17.1
	Prednisone 0.75 mg/kg/day	46	8.8	131.0	32.0	17.7
	Placebo	50	8.5	130.0	31.0	17.2
Karimzadeh 2012[20]	Deflazacort 0.9 mg/kg/day	14	7.1	116.6	20.4	NR
	Prednisone 0.75 mg/kg/day	12	7.4	122.1	23.3	
Bonifati 2000[21]	Deflazacort 0.9 mg/kg/day	10	8.6	NR		
	Prednisone 0.75 mg/kg/day	8	7.5			

BMI: body mass index, cm: centimeter, kg: kilogram, mg: milligram, N: total number, NR: not recorded

Observational Studies

We identified seven observational studies comparing deflazacort to prednisone (Joseph 2019, Shieh 2018, McDonald 2018, Lamb 2016, Bello 2015, Balaban 2005)[22-28] Five studies were conducted in the US, one in the United Kingdom (UK), and one was an international study. Differences in dosing regimens and outcome measures reported limit the comparability of these studies.

Joseph 2019 was a retrospective review examining fracture morbidity and growth using the UK NorthStar database. Although a total of 832 boys with DMD were evaluated in the study, only 193 boys were treated with either daily deflazacort or prednisolone, and the doses were not standardized. We summarize the results comparing only the 193 boys treated with daily deflazacort or prednisolone regarding their fracture incidence rate.[22]

Shieh 2018 was an observational study nested in the placebo arm of the ACT DMD trial (NCT01826487)[107] which looked at the efficacy and safety of ataluren as a treatment for DMD.[23] The study evaluated and compared the efficacy data analyzed for the 114 patients who were randomized to the placebo arm of the ACT DMD trial and received either deflazacort or prednisone (dosing frequency varied between daily and intermittent). Efficacy endpoints included change from baseline to 48 weeks of treatment in 6MWT, 4-stair climb, rise from supine, and 10-meter walk/run.[23]

McDonald 2018 was a multicenter, prospective cohort study that followed 440 patients (aged 2-28 years) diagnosed with DMD; patients were followed for 10 years.[24] The dosing regimen for patients treated with deflazacort and prednisone varied between daily and intermittent. While the comparison of steroid treatment versus no steroid treatment was the main outcome in this study, results were only stratified by type of daily steroid use (deflazacort or prednisone) for age at loss of ambulation, age at loss of ability to rise from supine, and age at loss of ability to complete the 4-stair climb.[24]

Both Lamb 2016 and Kim 2015 utilized data from the Muscular Dystrophy Surveillance Tracking and Research Network (MD Star*net*). Lamb 2016 evaluated growth patterns of 147 ambulatory boys (aged 2-12 years) with DMD who were treated with either deflazacort or prednisone.[25] In Kim 2015, the duration of corticosteroid treatment and its association with time to loss of ambulation was assessed among 477 patients. Short-term corticosteroid use was defined as 0.25 to three years, while long-term use was more than three years.[26] Within the short-term and long-term corticosteroid use, results for deflazacort and prednisone were stratified.

Bello 2015 studied 174 participants (aged 2-28 years) in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study who were treated with varying doses of daily deflazacort or prednisone. The study evaluated age at loss of ambulation and adverse events associated with steroid treatment in DMD.[27]

Balaban 2005 retrospectively reviewed the medical records of 30 boys (aged 12-15 years) diagnosed with DMD and treated with deflazacort or prednisone for more than two years, over a seven-year study period. The efficacy outcomes included functional measures such as time from supine to standing, time to climb four stairs, and time to run or walk 30 feet, pulmonary function as assessed by means of FVC, and back surgery for scoliosis.[28]

Baseline characteristics and additional information on the observational studies are detailed in Appendix D.

Clinical Benefits

The major outcomes reported in the three RCTs comparing deflazacort to prednisone were muscle strength, motor function, and pulmonary function. While Griggs 2016 reported on the different endpoints that assess motor function separately, Karimzadeh 2012 and Bonifati 2000 reported motor function as a composite measure.[19-21]

The observational studies included in this review evaluated motor function, pulmonary function, and time to or age at loss of ambulation.[22-28]

Muscle Strength

In Griggs 2016, for the primary outcome of change in muscle strength at 12 weeks as assessed by MRC, both deflazacort and prednisone improved MRC compared with placebo.[106] Compared with baseline, the increase in MRC with deflazacort was 0.15 (95% CI: 0.01 to 0.28) and with prednisone was 0.27 (95% CI: 0.13 to 0.41). Despite this being the primary outcome of the trial, no test of significance on this difference was reported. A secondary analysis looking at weeks 12 to 52 reported improvement in MRC in the deflazacort group (0.17) and a decrease in the prednisone group (-0.12), which was reported as statistically significant, although it was unclear whether the statistical plan allowed this analysis given the results of the primary outcome. An exploratory analysis looking at change in MRC from baseline to week 52 found no statistical difference between deflazacort and prednisone (0.39 vs. 0.23).

In Bonifati 2000, there was no significant difference in muscle strength as assessed by MRC between the deflazacort and prednisone treatment groups after one year of treatment (mean estimate from graph 0.91 vs. 0.87, respectively).[21] Both the deflazacort-treated participants and the prednisone-treated participants experienced improvements in muscle strength from baseline, while the natural history control experienced a worsening by one year of treatment (mean change from baseline estimated from graph 0.91 and 0.87 vs. -4.03).

Motor Function

In Griggs 2016, at 12 weeks, patients treated with deflazacort or prednisone had greater improvements in time from supine to standing, time to climb four stairs, and time to run or walk 30 feet compared with placebo; improvement with steroid treatment in the time to propel a wheelchair 30 feet was not statistically significant.[106] Results were not presented to allow appropriate comparisons between deflazacort and prednisone on these functional outcomes. The article states that from week 12 to 52, for these first three outcomes, the improvements were numerically higher with deflazacort than prednisone but not statistically significantly different, and that improvement from baseline to week 52 in the time to climb four stairs was greater with

deflazacort than prednisone (p=0.0461; significance level does not appear to have been adjusted for multiple testing).

In Karimzadeh 2012, motor function was assessed by a nine-point score based on 4-stair climb, time to rise from sitting position, and walking 10 meters (32 feet) on flat ground; with lower scores indicating better function. Patients treated with deflazacort had an improvement in the motor function score from baseline to 12 months, while those treated with prednisone showed worsening in motor function score (mean change: -0.57 vs. 0.25; p=0.001).[20] After 18 months of treatment, deflazacort-treated patients continued to show improvement in motor function score (mean change: -0.29) while those treated with prednisone had continued worsening (mean change: 0.75), however this difference was not statistically significant. Of note, those assessing motor function were aware of the treatment group.

Bonifati 2000 found no statistically-significant difference in motor function between participants treated with deflazacort and those treated with prednisone after one year of treatment.[21] Lower mean changes in functional scores from baseline indicated improvements for both treatment groups while the natural history control experienced a decline in motor function (mean changes estimated from graph -1.2 for deflazacort; -2.1 for prednisone; and 3.7 for the natural history control).

In addition to the RCTs, three of the seven observational studies we identified evaluated changes in motor function in patients on corticosteroids.[23,24,28] Motor function was generally assessed with 6MWT, 4-stair climb, time to rise from supine, and 30 feet or 10 meter walk/run test. In Shieh 2018, point estimates generally favored deflazacort, with statistically significantly better preservation of distance walked in the 6MWT and time required for the 4-stair climb; differences between the deflazacort- and prednisone-treated groups were 31.6 meters (95% CI: 0.22 to 62.94) for the 6MWT, -2.88 seconds (95% CI: -5.27 to -0.48) for the 4-stair climb, -2.60 seconds (95% CI: -5.20 to 0.01) in the time to rise from supine, and -0.09 seconds (95% CI: -2.07 to 1.89) for the 10 meter walk/run test.[23] McDonald 2018 found that deflazacort, when compared to prednisone, significantly prolonged the ability to rise from supine (13.10 years vs. 11.04 years; p=0.0114) and the loss of hand to mouth function (20.48 years vs. 17.77 years; p=0.01), while the difference for age at loss of the ability to climb four stairs was not statistically significant between the two groups (14.13 vs. 12.02 years; p=0.09).[24] Balaban 2005 found no differences between deflazacort and prednisone on motor function.[28]

Ambulation/Loss of Ambulation

Loss of ambulation was assessed in three observational studies.[24,26,27] Two of the studies found that deflazacort treatment significantly delayed age at loss of ambulation versus prednisone.[24,27] In McDonald 2018, the age at loss of ambulation was 14 years for deflazacort-treated patients versus

11.3 years for prednisone treated patients (p=0.01).[24] In Bello 2015, there was almost a three-year difference in median loss of ambulation between deflazacort and prednisone (p<0.001).[27] The third observational study, Kim 2015 reported the mean age at loss of ambulation in association with treatment duration.[26] The mean age at loss of ambulation was 9.6 years for those treated with short-term deflazacort and 9.4 years for those treated with short-term prednisone. For participants with long-term treatment, age at loss of ambulation was 12.6 years for the deflazacort group and 12.3 years for the prednisone group. Statistical difference between the groups was not reported.

Pulmonary Function

Two RCTs and one observational study assessed pulmonary function.[19,20,28] Griggs 2016 reported that there was no meaningful difference in change in FVC between deflazacort-treated participants and those treated with prednisone from week 12 to week 52, but no data were reported.[106] Karimzadeh 2012 found no abnormal vital capacity in both groups, though data were not reported.[20] Similarly, Balaban 2015 stated that differences in pulmonary function did not reach significance for either group.[28]

Harms

The majority of AEs reported in the RCTs were mild to moderate. The most commonly reported AEs observed in both deflazacort and prednisone treated patients were weight gain, Cushingoid appearance, hirsutism, and behavior changes (Table 3.2). Erythema, headache, central obesity, and mild infections were also commonly observed in one trial.[19] Serious AEs and AEs leading to trial discontinuation were more frequently reported in the prednisone-treated group compared to the deflazacort-treated group, although statistical significance was not reported (Table 3.2). Two deaths (one in the deflazacort group and one in the prednisone group) were reported in one of the RCTs.[106]

Weight-related AEs were less commonly reported in deflazacort-treated patients versus those treated with prednisone across all trials (Table 3.2). At 52 weeks, all three trials reported significantly less weight gain in the deflazacort-treated group compared to the prednisone-treated group.[19-21] For example, in the Griggs 2016 trial, deflazacort-treated patients had a mean weight gain of 5.1 kg compared to 8.5 kg in the prednisone group after 52 weeks of treatment (p<0.0001).[19] There was no statistically significant difference in discontinuation of steroids due to weight gain between prednisone and deflazacort (4.8% vs. 1.5% of deflazacort-treated patients). In Karimzadeh 2012, four patients treated with prednisone were excluded from the study at about 52 weeks of treatment due to uncontrollable weight increase despite consulting with a nutrition specialist. In addition, dose reduction due to weight related AEs was implemented in all prednisone treated patients (0.75 mg/kg/day to 0.3 mg/kg/day) compared to 21.4% deflazacort treated patients (0.9 mg/kg/day to 0.6 mg/kg/day).

Other important AEs observed in the RCTs were cataract and growth delay. Two trials reported a higher incidence of cataract in deflazacort-treated group compared to prednisone-treated patients (Table 3.2).[21,106] In one trial at 52 weeks, the point estimate of loss of height percentile was larger with deflazacort than prednisone (-11.4 vs. -7; p=0.22) and patients treated with deflazacort lost forearm length percentile compared with a slight increase in percentile in those treated with prednisone (-8.05 vs. 0.85; p=0.0011).[106] In one RCT, height percentile change was reported to be similar between deflazacort and prednisone at 52 weeks.[20]

Table 3.2. RCTs Comparing AEs of Deflazacort (DFZ) to Prednisone (PRED) at 52 weeks

Trial	Arm	N	Death, %	D/C due to AEs, %	Cushingoid, %	Weight Gain, %	Hirsutism, %	Behavior Change, %	Cataracts, %
Griggs 2016	DFZ	68	2	1.5	60	28	35	9	4.4
	PRED	63	2	5	78	35	44	14	1.6
Karimzadeh 2012	DFZ	14	NR	0	NR	NR	NR	NR	0
	PRED	12	NR	33	NR	NR	NR	NR	0
Bonifati 2000	DFZ	9	NR	0	55	11	55	66	22
	PRED	9	NR	11	50	15	50	62	11

AEs: adverse events, D/C: discontinuation, N: total number, NR: not reported

Long-term safety data related to deflazacort and prednisone use were also identified from three observational studies with follow-up duration of about four to 10 years.[24,27,28] These studies generally reported similar safety profiles for both deflazacort and prednisone, with weight gain, Cushingoid appearance, behavior changes, growth delays, fractures, and cataracts being the most frequently reported AEs (see Table 3.3). Similar to the RCTs, weight gain was less commonly observed and less severe in the deflazacort arms compared to the prednisone arms. Cataracts and growth delays were more frequently reported in deflazacort-treated patients than in those treated with prednisone.

In addition, we identified one retrospective study that assessed fracture burden in corticosteroid-treated boys with DMD.[22] The study showed that corticosteroid use was associated with an increased risk of fractures. Higher fracture incidence was observed among deflazacort-treated patients (1,367/100,000 patient-years; 95% CI: 796 to 2,188) compared to those treated with daily prednisolone (748/100,000 patient-years; 95% CI: 550 to 995). After adjusting for age, mean treatment dose, mobility status, and bisphosphonate use prior to the first fracture, deflazacort-treated patients had a 16-fold increased risk for first fracture (95% CI: 1.4 to 180.8; p=0.03), while the risk of first fracture was not increased for those treated with daily prednisolone.

A more detailed list of the AEs observed from all identified trials is provided in Appendix D.

Table 3.3. Long-Term AEs of Deflazacort and Prednisone from Observational Studies

Trial/Duration	Intervention	N	PY	Weight Gain, %	Cushingoid, %	Behavior Change, %	Growth Delay, %	Fracture, %	Cataracts, %
McDonald* 10 years	Deflazacort	107	877	5	6	3	5	1	3
	Prednisone	40	191	14	9	6	4	3	<1
Bello 3.8 Years ± 1.8 Years	Deflazacort	94	NR	63	72	33	60	25‡	29
	Prednisone	80	NR	67	50	30	27	22‡	5
Balaban 2005† 7 years	Deflazacort	12	NR	0	NR	8	NR	8	17
	Prednisone	18	NR	16	NR	17	NR	6	0

AE: adverse event, N: total number, PY: person-years
*% calculated as number of side effect/total person-years exposure
†Reports only serious AEs
‡Low Bone Mineral Density or Fracture

Exon-Skipping Therapies

Eteplirsen and golodirsen treatment results in very small increases in dystrophin. Extremely limited randomized data for eteplirsen did not show improvements in the 6MWT compared with placebo. No functional outcome results have been reported for golodirsen. Observational data comparing open label eteplirsen to matched or historical controls raise the possibility of improvements in motor and pulmonary function, including time to loss of ambulation. Harms of eteplirsen appear to be minor. No safety data were available to report for golodirsen.

Overview of Trials

Eteplirsen

Data to inform our assessment of eteplirsen were mainly drawn from four trials: Study 201, Study 202, Study 204, and Study 301.[29-31] Study 201 was a 28-week, single-center, US-based, blinded, placebo-controlled, Phase IIb RCT that enrolled 12 males aged seven to 13 years with a diagnosis of DMD and *DMD* gene amenable to exon 51 skipping.[29] Patients were randomly assigned to receive a once-weekly intravenous dose of 30 mg/kg of eteplirsen (n=4), 50 mg/kg of eteplirsen (n=4), or placebo (n=4) for the first 24 weeks. Afterwards, all patients were followed up for an additional four weeks of open label eteplirsen (patients in the placebo arm were rolled over to receive either 30 mg/kg (n=2) or 50 mg/kg (n=2) of eteplirsen). Eligible patients had to have stable respiratory function, be on a stable dose of oral glucocorticoid for at least 24 weeks prior to the start of the trial and be able to walk 180 to 440 meters on the 6MWT. Key baseline characteristics of the patients enrolled in Study 201 are presented in Table 3.4. The primary efficacy endpoint for the RCT was change in the percentage of dystrophin positive fibers at week 12 for the 50 mg/kg dose of eteplirsen and week 24 for the 30 mg/kg dose of eteplirsen. Of note, the 30 mg/kg weekly

dose of eteplirsen is the FDA approved dose. Other outcomes assessed included 6MWT, loss of ambulation, and pulmonary function.

Study 202 was a four-year open-label trial that enrolled all patients from Study 201.[30] The trial was designed to assess ongoing efficacy and safety of eteplirsen. Patients continued on the same dose of eteplirsen they received at the end of Study 201 (six patients on 30 mg/kg and six patients on 50 mg/kg).[30]

Study 204 was an open-label, multicenter study of male patients aged seven to 21 years diagnosed with DMD amenable to exon 51 skipping and who were minimally ambulatory (6MWT <300 meters) to non-ambulatory.[31] Patients had to have stable cardiac and respiratory function and had to either be stable on oral glucocorticoid treatment or not be on corticosteroid therapy for at least 24 weeks prior to the start of the trial. All patients received a once-weekly intravenous dose of 30 mg/kg of eteplirsen for 96 weeks followed by a safety extension for up to 48 weeks.[31]

Study 301 is an ongoing, multicenter, open-label, Phase III study of male patients aged seven to 16 years with a diagnosis of DMD that is amenable to exon 51 skipping.[31] Eligible patients were ambulatory with a 6MWT of 300 meters or more, on a stable dose of oral glucocorticoids prior to entering the trial, and had stable respiratory function. All patients received a once-weekly intravenous infusion of 30 mg/kg of eteplirsen for 96 weeks later followed by a safety extension. The primary endpoint was the change from baseline in the 6MWT at 96 weeks with a secondary endpoint that evaluated the change in the percentage of dystrophin positive fibers. Change in pulmonary function was an exploratory endpoint.[31]

Table 3.4. Baseline Characteristics of Eteplirsen RCT (Study 201)

Study	Drug	N	Mean Age, years	Mean Height, cm	Mean Weight, kg	6MWT, m
Mendell 2013[29]	Eteplirsen 30 mg/kg/week	4	9.3	130.5	34.8	355.3
	Eteplirsen 50 mg/kg/week	4	8.5	121.3	29.0	396.0
	Placebo	4	8.5	119.3	30.6	394.5

6MWT: 6-minute walk test, cm: centimeter, kg: kilogram, m: meter, N: total number

Golodirsen

The recently completed trial of golodirsen (SKIP-NMD) is a US-based, blinded, placebo-controlled, dose-escalation two-part Phase I/II RCT of male patients aged six to 15 years with a DMD diagnosis and *DMD* gene amenable to exon 53 skipping.[32] Eligible patients with stable cardiac and pulmonary function, and on a stable dose of corticosteroids for at least six months were included. In part one, 12 patients were randomized to receive once-weekly intravenous infusions at escalating doses of 4,

10, 20, 30 mg/kg of golodirsen or matching placebo for 12 weeks. Part two consists of an open-label period of all patients from part one and 13 newly recruited patients who are receiving once-weekly infusions of 30 mg/kg of golodirsen for up to 168 weeks. In parallel during part two of the trial, patients with *DMD* gene not amenable to exon 53 skipping, but met all other inclusion criteria, were also being followed up with no golodirsen treatment as an untreated control group up to 144 weeks.[32]

Part one primarily assessed safety and tolerability. In part two, the primary endpoints are change from baseline in 6MWT at 144 weeks and change in dystrophin protein levels at 48 weeks. Secondary endpoints include drug pharmacokinetics, change from baseline in FVC percent predicted, and change from baseline in dystrophin intensity at 144 weeks.[32]

Clinical Benefits

Dystrophin Production

Dystrophin production was assessed as the primary outcome in the completed RCT of eteplirsen (Study 201).[29] This was assessed at week 12 for the 50 mg/kg dose of eteplirsen and week 24 for the 30 mg/kg dose of eteplirsen. At week 12, there was no statistically-significant difference in change in dystrophin-positive fibers between patients receiving 50 mg/kg of eteplirsen and those on placebo.[29] However, by week 24, patients receiving 30 mg/kg of eteplirsen had a greater change from baseline in percentage of dystrophin positive fibers at compared to the placebo group (mean change in percent of dystrophin: 23% vs. -4%, mean difference = 27%, $p \leq 0.002$).[29,33]

Actual dystrophin levels, however remained very low in all patients. The patients in Study 201 were all treated for an additional four years with eteplirsen 30 mg/kg or 50 mg/kg.[30,34,35] After 180 weeks, 11 of the 12 patients underwent muscle biopsy to assess dystrophin levels, and the average level of dystrophin was 0.93% of that in healthy subjects; baseline dystrophin levels prior to treatment were not available. In another study, 13 patients treated with eteplirsen 30 mg/kg underwent muscle biopsy at baseline and after 48 weeks of treatment.[34,35] Among the 12 patients with evaluable results, mean dystrophin levels increased from 0.16% of the level in healthy subjects to 0.44% the level of healthy subjects (change of 0.28% of normal; $p=0.008$).

The ongoing open-label phase of golodirsen trial, SKIP-NMD, reports the change from baseline in dystrophin level for all patients who received 30 mg/kg of golodirsen. Mean baseline of dystrophin in the trial was reported to be 0.095% (Standard deviation [SD] 0.068) of normal. At 48 weeks, the mean level of dystrophin had increased to 1.019% of normal (SD 1.013), resulting in an absolute increase of 0.918% of normal ($p<0.001$).[32] A clinically meaningful change in level of dystrophin has not yet been established in humans. As such, the clinical significance of these results is not clear.

6MWT

Study 201 reported a mean reduction in 6MWT distance from baseline of 0.3 meters for patients on 50 mg/kg of eteplirsen and 128 meters for patients receiving eteplirsen 30 mg/kg, while those patients given placebo had a decrease of 26 meters from baseline at 24 weeks.[29] However, the investigators attributed the large decline in the meters walked in the 30 mg/kg eteplirsen arm to two patients who showed a rapid disease progression immediately after enrollment. After excluding these two patients, the adjusted mean change in 6MWT distance increased by 14 meters from baseline for the 30 mg/kg eteplirsen arm.[29] No statistical significance was reported between treatment arms.

For further comparative analysis, investigators matched the 12 patients receiving open-label eteplirsen during Study 202 to 13 age- and genotype-matched historical controls.[30] Data on the historical controls were obtained from two DMD natural history registries, with 186 patients. Patients in the registries who were receiving corticosteroid therapy at baseline and had both a baseline assessment and at least one post-baseline assessment on 6MWT were eligible to be included as controls. Only patients aged seven years and older with DMD amenable to exon 51 skipping (similar to the eteplirsen-treated patients) were included as matched controls (n=13).

Compared to the historical control group, eteplirsen-treated patients showed less decline in 6MWT by the second year (difference of 67 meters), and a larger statistically significant difference of 148 meters by the third year (p=0.0052) and 162 meters by the fourth year (p=0.0005) (Table 3.5). Of note, there was a lower incidence of loss of ambulation in the eteplirsen-treated group (two patients [17%]) compared to the matched control group (10 patients [77%]). Using a Kaplan-Meier analysis that accounted for missing data in the control group, the rate of loss of ambulation over four years was 17% in the eteplirsen group compared to 85% in the control group (p=0.011).[30,105] Results for Study 301 on 6MWT are not yet available.

Table 3.5. Eteplirsen versus Matched Control: 6MWT & Loss of Ambulation at Baseline to Year Four

Outcome	N	Arms	Baseline	Year 1	Year 2	Year 3	Year 4
6MWT Distance, Mean meters (SD)	12	Eteplirsen	363.2 (42.2)	305.8 (155.3)	295.9 (149.0)	263.1 (151.7)	196.3 (130.2)
	13*	External control	357.6 (66.8)	318.6 (94.2)	223.5 (145.4)	110.3 (136.2)	27.3 (90.5)
Loss of Ambulation, N (%)	12	Eteplirsen	--	2 (17)	2 (17)	2 (17)	2 (17)
	13*	External control	---	0	3 (23)	6 (46)	10 (77)

6MWT: 6-minute Walk Test, N: total number of patients

*Two historical control patients did not have data at all timepoints; one contributed until year one, and the second contributed until year two.

Pulmonary Function

Published literature suggests a linear decline of approximately 5% annually in the percent predicted forced vital capacity (FVC%p) of patients with DMD, regardless of corticosteroid treatment.[108-111] Eteplirsen-treated patients in the three open-label trials generally showed a slower decline.[31] In the open-label trial conducted among ambulatory DMD patients over four years (study 202), eteplirsen-treated patients had a decline of 2.19% annually in FVC%p.[31] In the second open-label trial that evaluated non-ambulatory DMD patients for two years (Study 204), patients on eteplirsen showed a decline of 3.66% annually in FVC%p.[31] Similarly, interim analysis from the ongoing Phase III open-label study (study 301) in ambulatory DMD showed a decline of 3.79% annually in the FVC%p.[31]

Investigators further compared the changes observed in these trials to a matched control group of glucocorticoid treated DMD patients aged 10 to <18 years drawn from a registry with mutations amenable to exon 51 skipping (n=20).[31] Data on matched controls were obtained from a prospective natural history studies of more than 400 DMD patients.[24] Respiratory assessments were conducted for all patients entering the natural history studies every three months for one year, at 18 and 24 months, and every year thereafter.[31] Compared to the matched control group, eteplirsen-treated patients had a statistically significant slower decline in the annual rate of FVC%p (Table 3.6).[31]

Table 3.6. FVC% Predicted in Patients Treated with Eteplirsen versus Matched Controls

Matched Control/Trials	N	Number of Observations	Baseline Mean	Mean Annual Change (SE)	Difference in Annual Change vs. Control, 95% CI	p-value
Matched Control	20	88	79.6 (13.3)	-6.00 (0.41)	reference	----
Study 201/202	12	132	96.9 (14.0)	-2.19 (0.71)	3.81 (2.19,5.42)	<0.001
Study 204	20	117	65.9 (16.6)	-3.66 (0.68)	2.34 (0.77,3.90)	0.004
Study 301	42	184	78.5 (15.7)	-3.79 (0.82)	2.21 (0.40,4.02)	0.017

CI: confidence interval, N: total number, SE: standard error

Harms

The majority of AEs observed in the clinical trials of eteplirsen were considered to be mild or moderate. AEs that occurred in two or more patients, and were more frequent in the eteplirsen arm in the Phase IIb RCT (study 201) included procedural pain, bladder disorder, contact dermatitis, balance disorder, hypokalemia, vomiting, and hematoma (Table 3.7).[34] One serious AE (fracture), which was considered not to be related to eteplirsen was observed in one patient during the subsequent open-label trial (Study 202). Other important AEs noted in eteplirsen-treated patients in Study 201/202 included changes in coagulation due to thrombosis in device that occurred in two patients, and two cases of transient urine protein elevation which resolved without intervention. There were no AEs leading to trial discontinuation, or deaths during the randomized controlled trial phase, and subsequent open-label trial.

Overall, eight severe AEs (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.[34] Except for the cardiomyopathy which occurred during a dose ranging trial of eteplirsen,[112] all were considered not to be related to the use of eteplirsen.[34]

No safety data were available from the Phase I/II trial of golodirsen at the time of this report.

Table 3.7. AEs Occurring in ≥2 Patients during Phase II RCT (Study 201)

AEs	All Eteplirsen (N=8), n (%)	Placebo (N=4), n (%)
Procedural Pain	4 (50)	3 (75)
Contact Dermatitis	2 (25)	0
Balance Disorder	3 (37.5)	0
Hypokalemia	4 (50)	2 (50)
Vomiting	3 (37.5)	0
Hematoma	2 (25)	1 (25)

AEs: adverse events, n: number, N: total number

3.4 Controversies and Uncertainties

Although there is evidence that corticosteroid treatment is beneficial for DMD patients, the optimal dosing, dosing regimen, and duration of therapy remain unclear. Relatively small clinical trials have provided only short-term efficacy data, even though long-term use of corticosteroids is the norm. Although observational studies have provided longer-term data, the heterogeneity of the DMD population, uncertainty about the natural history of the disease, variable dosing and outcome measures, and limited comparison data between corticosteroids leave a substantial gap in understanding the efficacy and adverse effects of long-term steroid therapy, particularly with respect to differences between deflazacort and prednisone. Additionally, there may be selection bias affecting the long-term observational studies of US patients receiving deflazacort, as deflazacort was not approved for use in the US until 2017. Prior to that time, patients desiring to take deflazacort had to import the drug from overseas with 100% out-of-pocket cost (approximately $1,000). Thus, those patients who were able to obtain deflazacort may have systematically differed from those taking prednisone in ways that may affect outcomes (e.g., socioeconomic status, family stability).

For the exon-skipping therapies, data are mainly limited to surrogate outcomes from very small trials, and the threshold for dystrophin expression sufficient for meaningful clinical improvement (e.g., significant motor improvement or delay in development of cardiac or respiratory conditions) has yet to be defined.[113] Thus, the clinical efficacy of exon-skipping therapies is still unclear. Additionally, the optimal time to begin therapy with exon-skipping drugs, long-term efficacy and adverse events have not been established. Quality of life data have also not been reported.

As discussed above, generating high-quality evidence for treatments for ultra-rare disease can be challenging and use of surrogate outcomes and historical controls may be required in assessing emerging therapies. However, while such study designs allow for greater feasibility in conducting trials, they also have significant potential shortcomings. Improvements in surrogate outcomes may be of uncertain clinical benefit if they do not have convincing human or animal evidence of clinical importance; historical controls can be subject 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.

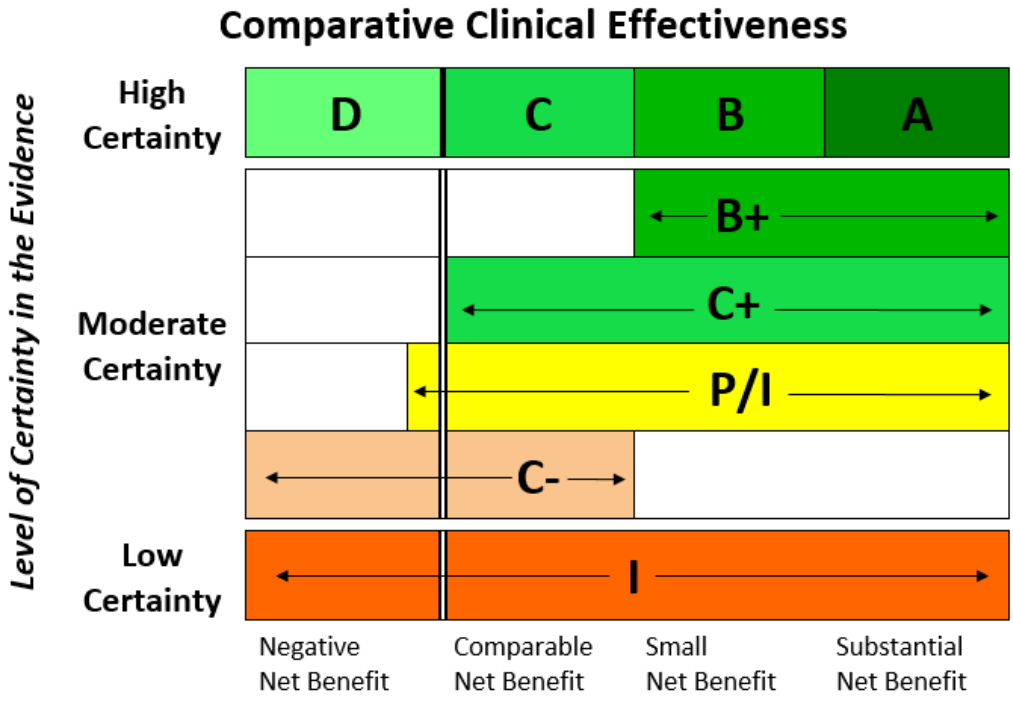
Standard functional outcomes (e.g., 6MWT) may not fully characterize the effects of drug therapy, since many functional outcomes are effort dependent and may have limited reliability in predicting an individual patient's clinical status. Additionally, current outcome measures may not adequately reflect a patient's daily functional status. Caregivers and patient groups expressed that, in terms of impact on quality of life and caregiving, the time a patient requires to complete the 6MWT may not be as important as whether the patient can complete the test at all. Additionally, for patients and caregivers, stabilization of function may be as important as improvement. These groups suggested that new measures that better capture the nuances of patient function are needed to more accurately assess outcomes.

One such area of interest to these groups is the development and validation of videos to assess changes in functional status. Videos may give a more complete picture of functional status by allowing for observation not only of whether a patient can perform a specific task (e.g., rise from supine) but also how the task is being completed (e.g., how easily does the patient accomplish the task? What compensatory mechanisms is the patient using?). Additionally, videos can be taken over time, allowing for direct comparison using the patient as his own control. However, until these video outcomes are validated and applied consistently across trials, their use remains limited. It should be noted that there appears to be a gap between currently reported trial outcomes and video evidence shared by patients, particularly for eteplirsen. Videos of patients on eteplirsen appear to show clinical improvement in function that was not reflected in the clinical trial outcomes. The reasons for this discrepancy are unclear, but possibilities include flaws in study design and execution, flaws in data collection during the trial, or non-systematic collection and scoring of video data. Additionally, a subset of patients may benefit substantially from the drug while others do not benefit at all, and choice of clinical outcomes during trials that are not sensitive enough to detect subtle changes in clinical status may help explain why individual patient outcomes may differ from the overall results of the trial. Novel trials designs such as "n of 1" trials, where patients serve as their own controls, may also help identify reasons for the discrepancy between patient observation and clinical trial outcomes.

3.5 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings independently for deflazacort compared to prednisone; and eteplirsen and golodirsen, each compared to both supportive care and corticosteroids alone for patients with DMD. As discussed elsewhere in the report, ICER acknowledges that generating high-quality evidence for emerging treatments for ultra-rare diseases can be challenging.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Deflazacort versus Prednisone

Deflazacort has been compared to prednisone in randomized trials in a small number of patients and for limited periods of time. These data as well as additional observational studies suggest that there may be some greater benefits on motor function with deflazacort, although not all data are consistent, and the size of the benefits may be small. Deflazacort has not been shown to improve pulmonary function outcomes compared with prednisone.

Given the many side effects of corticosteroids, the primary interest in deflazacort has been around reduced harms. Most data suggest less weight gain with deflazacort than prednisone, but also reduced growth. Behavioral/psychiatric side effects are of particular concern to caregivers, but the evidence is inadequate to conclude that these side effects are seen more frequently with prednisone than deflazacort. Many other steroid side effects have been evaluated with inconsistent comparative results. Overall, given the evidence on motor function and weight, we have moderate certainty that deflazacort has comparable or better net health benefits compared to prednisone ("C+").

Eteplirsen

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 benefit are observational with matched or historical controls and need to be confirmed in larger, ongoing trials. Furthermore, the main outcome reported, 6MWT, 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.

Golodirsen

The data for golodirsen are even more limited than for eteplirsen and demonstrate only small increases in dystrophin levels. Functional outcomes and safety data have not been reported. Thus, the evidence on golodirsen is insufficient ("I").

4. Long-Term Cost Effectiveness

4.1 Overview

The objective of this economic evaluation was to assess the cost effectiveness of deflazacort, eteplirsen, and golodirsen for treating patients diagnosed with DMD in the US. Specifically, DMD treatment with deflazacort and supportive care was compared to using prednisone and supportive care. Eteplirsen and golodirsen were evaluated as add-on therapy to corticosteroids and supportive care versus corticosteroids and supportive care alone. Since the societal costs associated with DMD were estimated to be substantial relative to the condition's health care sector costs for prednisone and deflazacort, the base-case analyses for deflazacort were reported from health care and modified societal perspectives, aligning with ICER's Value Assessment Framework for Ultra Rare Diseases. For eteplirsen and golodirsen, there was insufficient evidence to model specific treatment effects. With the available price for eteplirsen, the model was used to determine any threshold treatment effects whereby the treatment would be cost-effective at broad range of cost per QALY willingness-to-pay thresholds. While golodirsen was also considered in this economic evaluation, in the absence of a treatment effect or price for this therapy, an analysis comparing it to corticosteroids and supportive care alone was not included. However, if one assumes that golodirsen will have the same costs as eteplirsen, then the threshold analyses would be the same for golodirsen as for eteplirsen (see below).

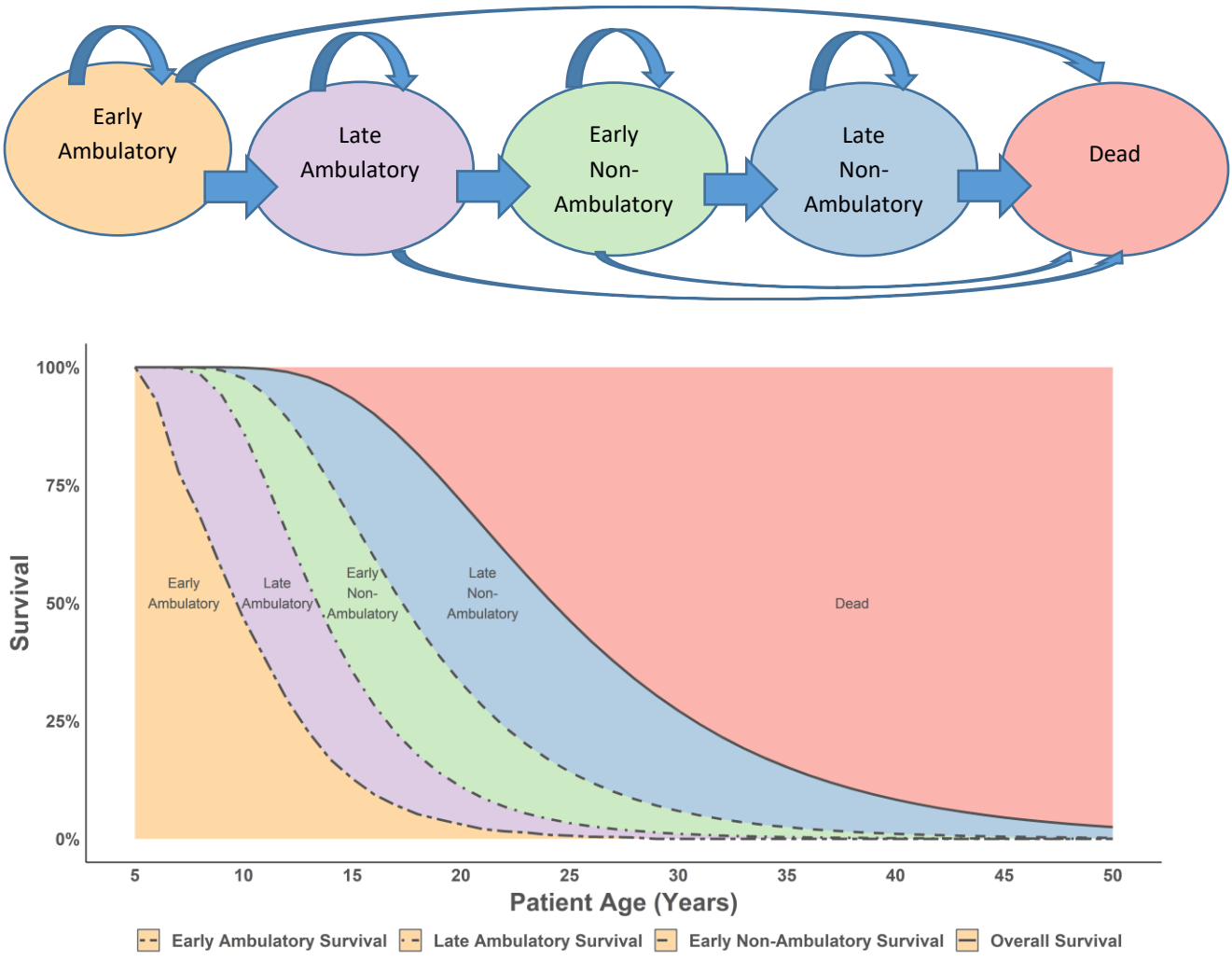
4.2 Methods

A *de novo* multi-state partitioned survival model was developed for this evaluation, informed by key clinical trials, cohort studies, and prior relevant studies related to economic modeling in DMD.[24,36-40] A partitioned survival model was chosen as it was the best fit with the underlying data available for DMD patients, particularly as informed by long-term studies that have tracked loss of ambulation by age. Though information on mortality by age is more limited, the data are still best summarized by Kaplan Meier (KM) type survival curves.

The model focused on an intention-to-treat analysis using a hypothetical cohort of patients with DMD that begin treatment at the age of five years. The baseline survival curves that are used to partition patients into the relevant health states, shown in Figure 4.1 below, were based on a prior comprehensive analysis of international clinical trial data involving steroid treatment for DMD. We made key structural changes to the model from the draft evidence report to this version of the report in response to public comments received. The main structural change that took place was to increase the number of health states in the model to better reflect DMD progression. We went from three health states (ambulatory, non-ambulatory, and death) to five health states (early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory, and death). During

internal review, we also updated drug dose and utility value inputs which will be described further below. The proportions of ambulatory patients in early and late stages were based on a published modeling study which used definitions of those stages most consistent with the original survey data to inform utilities and supportive care costs in the model.[36,37] The model incorporates best available annual estimates of costs and utility scores associated with each DMD health state for US patients from a prior study of national DMD registries.[10] In addition, established SAEs were accounted for in the model for deflazacort and prednisone as described below. The base-case model was used to project total costs, life years (LYs), and quality-adjusted life years (QALYs) over a lifetime time horizon as well as to determine threshold treatment effects. Costs and outcomes were discounted at 3% per year.

Figure 4.1. Model Framework



Key Model Choices and Assumptions

Medical and non-medical costs, patient utility, and caregiver utility depended on the patient's health state and were modeled on an annual basis. SAEs could also impact utility and costs as described below. Treatment effects were modeled as rightward shifts of all the survival curves related to stages of ambulation, non-ambulation, and death, and/or if there was evidence of having different rates of SAEs.

Our model included several assumptions stated below in Table 4.1.

Table 4.1. Key Model Assumptions

Assumptions	Rationale
The model starts with patients in the early ambulatory health state at the age of five years. They then transition into one of the following health states: late ambulatory, early non-ambulatory, late non-ambulatory, and death. The transition rates are based on survival curves from prior analyses, which themselves were based on international clinical trial data and historical data for patients diagnosed with DMD and receiving steroids.[37]	The best available estimate for current health trajectories associated with patients on prednisone was a prior analysis projecting the health states of DMD patients on steroids.[37] Those projections matched generally with age at loss of ambulation found in MD Star*net* for US patients.
Costs and utilities for the early and late ambulatory and early and late non-ambulatory health states were based on prior survey results.[36] Proportions of patients in these states following treatment in the model were based on parallel shifts of all the survival curves.	There was no evidence-based mechanism for relating treatment effects to the proportion of years spent in early and late ambulation or early and late non-ambulation. In the absence of any evidence, we assumed constant proportions for years spent both in early and late ambulation and early and late non-ambulation.
The proportion of patients in early and late ambulation were informed by proportions by age of ambulatory and non-ambulatory patients considered as early and late as defined in a prior model.[36] Those definitions were based on clinical expertise and available historical data related to the progression of DMD.[36,40,114]	Early and late ambulatory stages are not explicitly defined in the international trial data. In the absence of these data, we applied the proportions by age reported in the original published model structure built.[36] This definition matches most closely with the survey of costs and utilities used in the model.[36] .
Treatment effects in time to non-ambulation were modeled using direct rightward shifts (i.e., parallel shifts) in the non-ambulation survival curve and the mortality curve being used in the model.	There is insufficient evidence to establish treatment effects on time in ambulation beyond rightward shifts in the existing curves. In the absence of long-term data, rightward shifts in the ambulation curve along with equivalent shifts in the mortality curve offered a reasonable upward bound approximation of a treatment effect. A similar assumption was made in one of the few past models of DMD.[38] The estimated

Assumptions	Rationale
	shift was equal to 2.7 years in the ambulatory and non-ambulatory health states based on a recent observational study in DMD, which we rounded up to three years.[24]
There was insufficient evidence to estimate a treatment effect for eteplirsen, therefore scenarios were estimated which eliminated the need for supportive care costs to explore cost-effectiveness implications with the most favorable possible scenarios for eteplirsen at its given price.	Eteplirsen resulted in very small increases in dystrophin and no improvements in functional outcomes such as the 6MWT.[29-31]. Therefore, to model potential cost effectiveness we explored potential scenarios in which eteplirsen resulted in significant QALY gains, given its current price.
The proportion of supportive care costs from a societal perspective made up by supportive care costs from a health care sector perspective was the same in the ambulatory and non-ambulatory health states.	Cost estimates by specific category that allow separation of costs by perspective (health care and societal) were not available across health states. Changes in total direct costs were available across health states by country and the ratio of non-ambulatory to ambulatory in average total costs for the US was used to adjust each of the categories of costs across health states.[10] This means the number for supportive care costs by health state is accurate according to the survey for the societal level estimates. Though representative overall, it is still possible that the health care sector perspective costs may be over or underestimated by specific health state.
Patients are diagnosed and begin treatment at five years of age.	Available evidence suggested diagnosis occurs around five years of age (MD Star*net*) and patients do best with long-term treatment with steroids beginning at age five.[14]
SAEs (weight gain, Cushingoid, fractures, cataracts) related to prednisone and deflazacort each resulted in a disutility of 0.05 per annual cycle for the relevant proportion of patients according to the rates reported in the same study showing the largest available treatment effect.[24]	The few available estimates of disutility for any of the AEs were less than 0.05.[115-119] Hence, as a conservative approach, we believed 0.05 would be a reasonable disutility as an upper bound on potential QALY effects from SAEs.

Target Populations

The population of focus for the economic evaluation was patients in the US diagnosed with DMD. For model projections related to eteplirsen and golodirsen, the target population was US DMD patients eligible to receive those treatments.

Interventions

The list of interventions was developed with inputs from patient organizations, clinicians, manufacturers, and payers. The list of interventions is presented below:

- Deflazacort
- Eteplirsen

Comparators were chosen to best reflect real-world treatment decisions likely to be made by clinicians. The base-case analysis considered the comparison between deflazacort and supportive care and prednisone and supportive care. Eteplirsen was separately considered as additional treatment to corticosteroids and supportive care.

Input Parameters

Clinical Inputs

Given multiple studies where it was not possible to quantitatively synthesize by meta-analysis or NMA, we selected evidence-based results for the primary treatment effect that was most favorable to deflazacort and served as a conservative approach.[24] For consistency, results from the same study also informed the modeling of the impact of SAEs as they were also relatively favorable to deflazacort.[24]

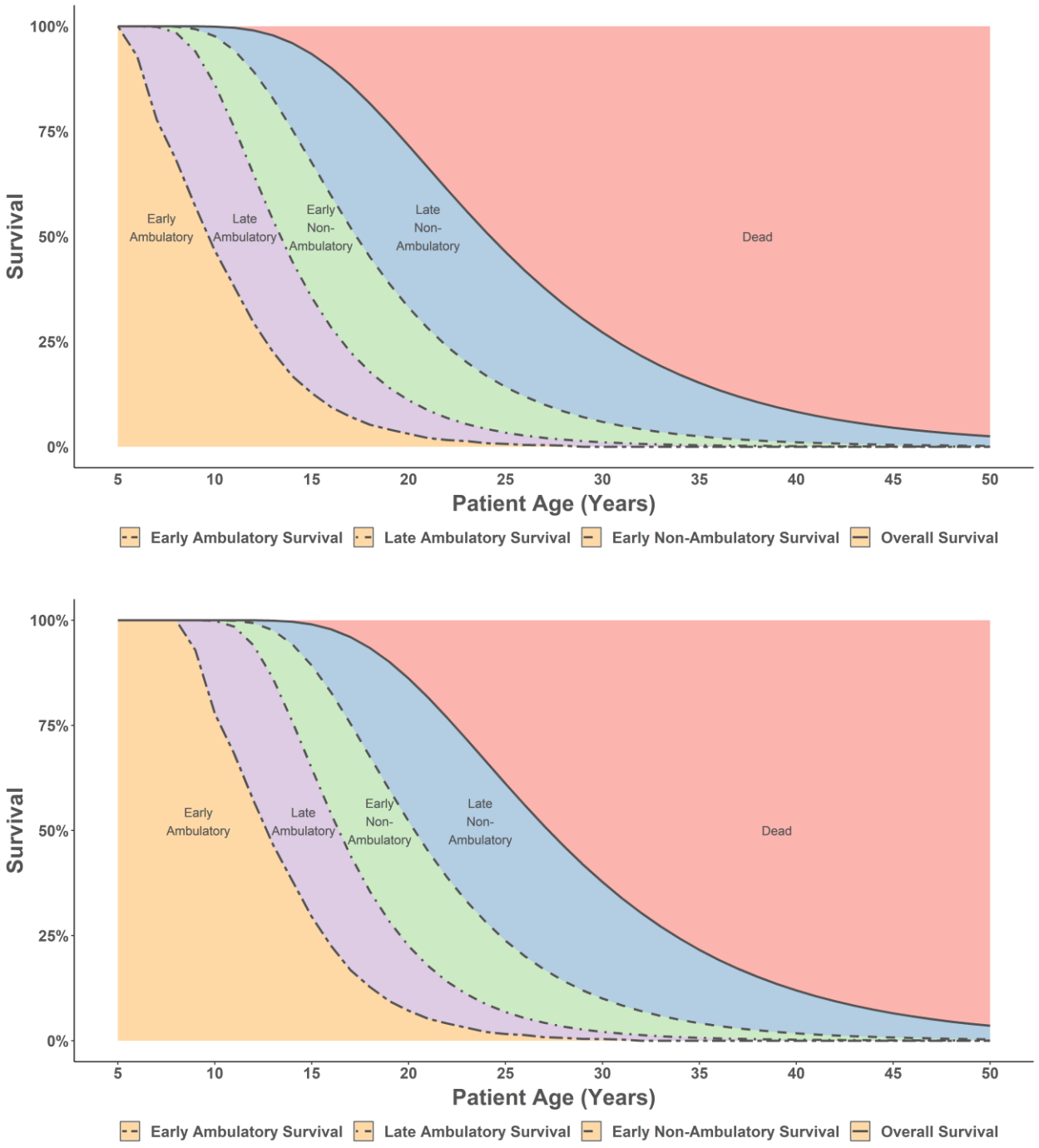
Transition Probabilities

Survival curves on time to non-ambulation and time to death for patients on steroids were based on a recent research effort that measured expected patient outcomes for DMD patients on corticosteroids based on international trial data that included sufficient Kaplan-Meier (KM) curve evidence.[37] In that study, KM curves for loss of ambulation as well as early and late non-ambulation and death were projected for steroid users based on the following: 1) available survival data for DMD patients with and without steroid use, and 2) past published efforts at modeling DMD.[36,37] Available KM curves were adjusted for censoring and converted to individual patient data and fit with functional forms to derive hazard rates for loss of ambulation with steroid use. The mortality curves were then fit to match mortality patterns seen in registry data with assumed increases in the hazard of death beyond 35 years of age.[36,40,114] We digitized these curves and fit log-normal survival

functions to them (see below for more details). The resulting curves, shown in Figure 4.1 above, were used to inform transitions between health states in the base-case model. Note that the prior study used for estimating supportive care costs and utility scores distinguished early and late ambulatory based purely on age-related definitions and we used those proportions by age to project early and late ambulatory stages in the base-case analysis .[36,37] Our model also uses parallel rightward shifts in early and late states of ambulation and non-ambulation, as there is currently no evidence for how treatments impact the relative time spent in early or late ambulation or in early or late non-ambulation. The early and late stage portions of ambulation and non-ambulation are based fundamentally on the relative proportion of patients in early and late ambulatory and early and late non-ambulatory states, as seen in the study we used for the US health state-specific costs and utilities,[10] described further below. We assumed that when treatments extend time to loss of ambulation, they consistently delay all progression of the disease such that there are parallel rightward shifts in all the survival curves relating to early/late ambulatory, and early/late non-ambulatory states. These likely serve as very favorable assumptions towards the treatments being modelled.

In building the model, we first fit the overall ambulation and early and late non-ambulation curves. Specifically, we digitized the curves from this past study[37] and fit a variety of parametric curve functions.[120] The potential model curves included the distributional forms Weibull, exponential, log-normal, log-logistic, gamma, and Gompertz. The final parametric functions were then selected based on the best model fit using Akaike information criterion (AIC) values, available in Appendix Table E2. A curve dividing early and late ambulation was then included based on proportions by age in a prior published modeling study[36] that characterized those stages based on definitions that were consistent with previous evidence.[40,114] Costs and utilities by health state were informed by previous studies.[10,36] Following generation of the base curves, the curves used to model deflazacort were generated using parallel rightward shifts of all the curves. Figure 4.2 below illustrates the resulting curves for prednisone and deflazacort by age.

Figure 4.2. Comparator Prednisone (Top) and Deflazacort (Bottom) Survival Curves* for the Likelihood of Being in Each State in the Model



*Survival curves in the comparator arm (top) are digitized from a prior analysis.[37] The bottom figure illustrates the three-year rightward shift for the treatment effect applied to deflazacort.

Mortality

Age-dependent mortality for patients with DMD was estimated based on the survival curves described above and illustrated in Figure 4.2. These estimates aligned generally with data on age at loss of ambulation, survival data in the US (MD Star*net*), and the modeled mortality in a prior DMD analysis, although there may be some overestimation of survival in the tails (see scenario analyses and limitations below).[36]

Treatment Effects

The available trial data were not suitable for an NMA nor was it possible to conduct a meta-analysis from any of the studies on DMD treatments available in the literature. The treatment effect used in the base-case model for deflazacort relative to prednisone came from a selected recent cohort study that contained the largest evidence-based treatment effect for deflazacort relative to prednisone.[24] Specifically, the study included evidence that the median age of loss of ambulation for prednisone users was 11.3 years and for deflazacort it was 14 years.[24] We incorporated this finding into our model by using the base curves for prednisone and shifting the ambulatory curve rightward by three years (14 minus 11.3 years, rounded up) for deflazacort. Further, in the absence of evidence, we shifted the mortality curve for deflazacort by the same three years. Other treatment effects were explored in scenario analyses and threshold analyses.

For eteplirsen, there was insufficient evidence to establish a treatment effect. We thus used the model to determine whether there were potential treatment effects—modeled by shifting the ambulatory and mortality curves rightward for 10, 20, and 40 years—to explore resulting incremental cost-effectiveness ratios given its current price.

Adverse Events

In our preliminary search within the published literature, we found several cohort studies pertaining to SAEs related to deflazacort and prednisone. As stated earlier, there were insufficient data to conduct an NMA or meta-analysis. Hence, for deflazacort and prednisone we used results related to significant differences in SAEs from a recent large cohort study selected because it contained upper-bound evidence of treatment effects for deflazacort adopted in the base case.[24] Specifically, the base-case analysis comparing deflazacort and prednisone considered rates of weight gain, Cushingoid appearance, behavioral change, cataracts, and fractures (see Table 4.2).

There were no reported significant SAEs for eteplirsen; therefore, none were included in the model.

Table 4.2. Annual SAE Rates for Prednisone and Deflazacort

AE	Mean Rate (Low-High*) for Prednisone	Mean Rate (Low-High*) for Deflazacort	Source
Cataracts	0.001 (0.000-0.001)	0.003 (0.002-0.004)	McDonald, 2018[24]
Cataract Surgery	0	0.069 (0.055-0.083)	Rice, 2018[121]
Weight Gain	0.015 (0.120-0.017)	0.006 (0.004-0.007)	McDonald, 2018[24]
Cushingoid	0.009 (0.007-0.011)	0.007 (0.005-0.008)	McDonald, 2018[24]
Behavior Change	0.006 (0.005-0.007)	0.003 (0.002-0.004)	McDonald, 2018[24]
Fractures	0.003 (0.003-0.004)	0.001 (0.001-0.002)	McDonald, 2018[24]

SAE: serious adverse event

*The low to high rates reflect 20% decreases and increases, respectively, assumed as bounds in potential variance.

Treatment Discontinuation

Despite clinical recommendations to continue treatment, there is evidence that a substantial proportion (39%) of patients discontinue steroid treatment upon reaching a non-ambulatory health state.[122] We used this estimate of steroid discontinuation in the non-ambulatory health states in our base-case analysis.

Health State Utilities

Health state utilities were based on a prior study that included survey data on US DMD patients (see Table 4.3).[10] Utility scores based on the Health Utility Index (HUI; proxy assessed by the primary caregivers) were included and separated into early and late ambulatory and early and late non-ambulatory in this study. Caregiver utilities were elicited from the EuroQol EQ-5D-3L.[10]

Table 4.3. Ambulatory and Non-Ambulatory Health State Utility Scores

Health State	Patient Utility	Caregiver Utility*	Source
Early Ambulatory	0.730	0.845	Landfeldt 2014, 2017[10,36]
Late Ambulatory	0.640	0.839	Landfeldt 2014, 2017[10,36]
Early Non-Ambulatory	0.210	0.784	Landfeldt 2014, 2017[10,36]
Late Non-Ambulatory	0.180	0.810	Landfeldt 2014, 2017[10,36]

*Used in Scenario Analyses #3 and #4

Disutility of Adverse Events

There was a paucity of utility-related estimates in the literature for these SAEs and none specifically were recorded in children or adolescents. Further, available estimates of these events in the literature suggested disutilities of less than 0.05.[117-119] Hence, as a conservative approach, we used an assumed disutility of 0.05 per SAE per year based on the proportion of patients with each of the SAEs in the same large recent cohort study of DMD patients that was used to inform the overall treatment effect for deflazacort.[24]

Drug Utilization

Drug utilization was based on recommended treatment guidelines as outlined in Table 4.4.

Table 4.4. Drug Doses Used in the Models

Generic Name (Brand Name)	Dose	Approval Status	Source
Prednisone	Approximately 0.75 mg/kg/day administered orally	Generic, used off label	Griggs, 2016[106]
Deflazacort (EMFLAZA®)	Approximately 0.9 mg/kg/day administered orally	Approved	FDA Label[123]
Eteplirsen (EXONDYS 51™)	30 mg/kg/week administered by a 35-60 minute IV infusion	Accelerated approval contingent on verification of clinical benefit	FDA Label[124]

FDA: Food and Drug Administration, IV: intravenous, kg: kilogram, mg: milligram, mL: milliliter

Cost Inputs

The model included drug costs, health state specific costs such as supportive care, and the cost of AEs. Additionally, available societal perspective costs were included in the modified societal perspective described further below.

Drug Costs

All prices were derived using guidance provided in the ICER Reference Case. The net pricing estimates for deflazacort from SSR Health, LLC, were not available. Hence, we used the Federal Supply Schedule (FSS) price for deflazacort.[125] Specifically, we calculated its price based on its tablet and suspension forms. For prednisone, since numerous generic forms are available in the US market, we used its average generic price across different dosing strengths of its oral tablet formulation. Given that eteplirsen is often administered in a hospital, physician's office, or home setting, we expected it to have a price mark-up. We defined this mark-up as the average wholesale price (AWP) minus 15% as seen for specialty drugs.[41] Drug dosing is weight-based and was varied each year in the model according to available estimates of weight by age for DMD patients in the US.[126] Table 4.5 shows annual treatment cost estimates for a 40 kg patient. Note that in the model, prednisone and deflazacort doses are capped when patients reach body weight of 40 kg to match clinically-recommended maximum doses.[14] The cost estimate for eteplirsen is presented for a 40 kg patient for consistency. At age 20 (70 kg), weight was assumed to remain constant for the remainder of the patient's lifetime, and therefore dosing for eteplirsen was capped at 70 kg.

Table 4.5 Drug Costs Used in the Model

Intervention (Dosage)	Cost per mg	Annual Treatment Cost	Source
Prednisone (0.75mg/kg/day)	$0.05/mg	$550*	Red Book[41]
Deflazacort (0.9mg/kg/day)	$6.19/mg	$81,400*	Federal Supply Schedule, 2019[125]
Eteplirsen (30 mg/kg/week)	$16/mg	$1,002,000*	Red Book†[41]
Golodirsen	N/A	N/A	

AWP: average wholesale price, FSS: Federal Supply Schedule, kg: kilogram, mg: milligram, mL: milliliter, N/A: not applicable

*These estimates are for a 40 kg patient. Actual costs in the model will vary by expected weight based on the patient's age.

†Marked-up price is calculated as AWP-(15%*AWP) when the drug is administered at a hospital/physician's office.

Note: There was a discrepancy in annual costs between the draft and final report for deflazacort ($62,900 vs. $81,400, respectively) and eteplirsen ($892,000 vs. $1,002,000, respectively). The discrepancy was due to a calculation error related to the annual dose.

Non-Drug Health Care Costs

The health state-specific supportive care costs were based on a previous cross-sectional cost study that included US-specific estimates.[10] This original survey-based study provided annual societal cost estimates by health state for the US.[10] Specifically, we digitized the reported per-patient annual costs[10] for each of the four health states: early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory.[10] This same study also provided health care sector costs overall relative to societal costs, but those results were not reported by health state. Hence, in modeling health care sector supportive care costs we assumed that a constant proportion of societal costs were made up by specific categories of costs available from the underlying survey study across health states.[10] Specifically, ratios of total annual costs in the early and late ambulatory and early and late non-ambulatory health states, all relative to the overall average total costs, were used to project each of the detailed categories of costs to the early and late ambulatory and early and late non-ambulatory health states.[10]

Health care sector perspective costs included direct non-medication health care costs, costs of medications (these include numerous medication categories and are viewed in the model as not including the primary treatment costs), and covered costs of aids and devices. The societal costs of illness included all the reported cost categories (see Table 4.6 and Table 4.7 below for the costs used by category).[10]

Table 4.6. Annual Health Care Sector Supportive Care Costs by Health State

Costs	Early Ambulatory Mean [95% CI]	Late Ambulatory Mean [95% CI]	Early Non-Ambulatory Mean [95% CI]	Late Non-Ambulatory Mean [95% CI]	Source
Direct Medical (Non-Medication)	$18,629 [$15,206, $24,300]	$18,462 [$15,069, $24,082]	$27,304 [$22,286, $29,071]	$36,570 [$29,849, $47,702]	Landfeldt 2014[10]
Medications	$1,656 [$1,376, $2,168]	$1,641 [$1,363, $2,148]	$2,427 [$2,016, $2,640]	$3,250 [$2,701, $4,255]	Landfeldt 2014[10]
Aids and Devices	$2,296 [$1,798, $2,970]	$2,275 [$1,782, $2,944]	$3,365 [$2,635, $4,353]	$4,506 [$3,529, $5,830]	Landfeldt 2014[10]
Total Health Care Sector Costs	$22,581 [$18,379, $29,438]	$22,378 [$18,214, $29,174]	$33,096 [$26,938, $43,146]	$44,326 [$36,079, $57,788]	Landfeldt 2014[10]

CI: confidence interval

Table 4.7. Annual Societal Supportive Care Costs by Health State

Costs	Early Ambulatory Mean [95% CI]	Late Ambulatory Mean [95% CI]	Early Non-Ambulatory Mean [95% CI]	Late Non-Ambulatory Mean [95% CI]	Source
Non-Medical Community Services	$6,087 [$4,823 $7,831]	$6,032 [$4,780, $7,761]	$8,922 [$7,069, $11,477]	$11,949 [$9,468, $15,372]	Landfeldt 2014[10]
Informal Care	$10,694 [$9,647, $11,942]	$10,598 [$9,560, $11,835]	$15,674 [$14,139, $17,503]	$20,993 [$18,963, $23,443]	Landfeldt 2014[10]
Indirect Cost of Illness	$17,237 [$14,790, $19,773]	$17,083 [$14,657, $19,596]	$25,264 [$21,677, $29,981]	$33,837 [$29,033, $38,815	Landfeldt 2014[10]
Out-of-Pocket Costs for DMD-Related Home Alterations and Other Uncovered Equipment	$4,047 [$3,170, $5,237]	$4,011 [$3,141, $5,190]	$5,932 [$4,645, $7,675]	$7,945 [$6,222, $10,280]	Landfeldt 2014[10]
Total Societal Costs	$38,066 [$32,429, $44,783]	$37,725 [$32,138, $44,381]	$55,792 [$47,530, $65,636]	$74,725 [$63,659, $87,909]	Landfeldt 2014[10]

CI: confidence interval, DMD: Duchenne muscular dystrophy

Costs Associated with Adverse Events

For cataracts for each year, we included literature-based cost estimates for an office visit and for cataract surgery for the small proportion of patients for whom this is applicable[127] and inflated them to 2018 dollars as per the ICER Reference Case. We also incorporated, annually, literature-

based cost estimates for fractures (Diagnosis-related group (DRG) 535).[128] For weight gain, Cushingoid appearance, and behavioral change, as there were no available literature-based estimates of costs, we assigned the cost of a standard physician office visit (Current Procedural Terminology (CPT) Code 99213).[129] See Table 4.8.

Table 4.8. Adverse Event Costs per Year

Adverse Event	Base-Case Cost [Range used in PSA]*	Source
Cataracts	$75 [$38-$113]	CPT99213[129]
Cataract Surgery	$3,434 [$1,717-$5,152]	Rice, 2018[130]
Weight Gain	$75 [$38-$113]	CPT99213[129]
Cushingoid	$75 [$38-$113]	CPT99213[129]
Behavioral Change	$75 [$38-$113]	CPT99213[129]
Fractures	$7,661 [$3,831-$11,492]	DRG 535[128]

CPT: Current Procedural Terminology, DRG: diagnosis-related group

*Low and high values were 50% and 150%, respectively, of the base-case cost as there were no available confidence intervals.

Base-Case Analyses

Our base-case analyses included total costs, QALYs, and life years (LYs) gained, and incremental results in the form of cost per QALY, cost per LY, and cost per additional year in ambulation for deflazacort versus prednisone. These calculations were performed using a health care sector perspective and a modified societal perspective.

Summary of Assumptions Favorable to Deflazacort in the Base Case

To provide a conservative estimate for the cost effectiveness of deflazacort, we have incorporated the following favorable assumptions in the base-case analysis:

1. A treatment effect that shifts the early and late ambulation and early and late non-ambulation survival curves by approximately three years. This is the largest treatment effect seen in any study and is rounded up.[24]
2. Relatively favorable SAE prevention results sourced from the same study that reported the relatively large treatment effect.[24]
3. Relatively large disutilities for SAEs associated with both prednisone and deflazacort compared to available estimates in the literature. As deflazacort had lower overall rates of SAEs than prednisone, this assumption would be more beneficial to deflazacort.

Sensitivity Analyses

We conducted deterministic one-way sensitivity analyses of the base-case model comparing deflazacort to prednisone to identify the key drivers of model outcomes using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section (see Appendix E for more detail).

Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 10,000 simulations and calculating 95% credible range estimates for each model outcome based on the results (see Appendix E for more detail). For the survival curves, we used the best fitting parametric survival curve and corresponding Cholesky matrix to inform the relevant underlying distributions. Because the treatment shift effect of three years was viewed as an upper bound, we left that fixed in the probabilistic analysis, although it was varied in the deterministic analysis. For the other inputs, various distributions were selected to best model potential uncertainty including gamma and log-normal distributions for costs, and beta distributions for utilities.

Scenario Analyses

We conducted several scenario analyses in the base-case deflazacort versus prednisone model to explore potential variance of the outcomes depending on 1) the dose of the drugs, 2) the impact of adding hypothetical sources of additional treatment gains in the form of large treatment effects within ambulatory and non-ambulatory health states, and 3) including consideration of spillover health effects to caregivers. Each of these scenarios tested changes in model assumptions and inputs that were favorable to deflazacort in potential ways beyond the already favorable assumptions listed above for the base case. Scenario 1 changes the dose of the drugs to lower amount that could be clinically viable. Scenario 2 explores the impact of having deflazacort essentially eliminate the late stage of ambulatory and non-ambulatory which would be the biggest possible shift in the relative proportions of early and late within ambulatory and non-ambulatory that could be associated with deflazacort. Finally, since the patients are children and require caregivers, we also included scenario analyses from the modified societal perspective (which already includes consideration of costs to caregivers) that add modeled QALY gains of the caregivers related to the treatment effects to the already modeled QALY gains of the patients. Since patients are likely to have one or two caregivers, we included a scenario for each of those situations. The following specific scenario analyses were run:

1. The model was run assuming lower doses of the underlying steroids. Specifically, we reduced the doses of the treatments by approximately 25% to conform with a prevalent dose seen in a recent cohort study.[23]
2. The model was run using early ambulatory and early non-ambulatory costs and utilities[10] for ambulatory and non-ambulatory patients on deflazacort with no change to prednisone.

3. The model was run using a modified societal perspective including estimated utility gains of the patient and one caregiver as additional costs to caregivers have already been included in the base-case modified societal perspective.
4. The model was run using a modified societal perspective including estimated utility gains of the patient and two caregivers.

Additionally, to explore the potential implications of upward biased errors in the tails of the curves in the model, we ran the model for 45 cycles assuming 100% mortality at age 50 years.

Threshold Analyses

We performed the following threshold analyses:

1. We varied the cost of deflazacort to achieve willingness-to-pay thresholds between $50,000 to $500,000 per QALY and LY gained ($50,000, $100,000, $150,000, $300,000, and $500,000).
2. We assumed that eteplirsen would cause no SAEs and shift time to loss of ambulation and death rightward by 10, 20, and 40 years. These were each done from a health care sector perspective and a modified societal perspective.
3. Finally, we calculated an incremental cost-effectiveness ratio for eteplirsen if it shifted the ambulatory and mortality curves by 40 years, restored patient and caregiver utilities to perfect health, and eliminated the need for supportive care from both a health care sector and modified societal perspective.

Model Validation

We used several approaches to validate the model. First, we presented preliminary model methods to PTC Therapeutics (the manufacturer of eteplirsen declined to participate) and selected patient groups, and subsequently sent draft methods and results to clinical expert reviewers for this report. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We also performed model verification by internal reviewers.

4.3 Results

Base-Case Results

The total cost and outcome results of the dual base case are reported in Table 4.9 and Table 4.10, and incremental cost-effectiveness ratios are reported in terms of QALYs, LYs, and years in ambulation gained in Table 4.11. Deflazacort use resulted in more QALYs and LYs gained compared

to prednisone use, but at higher costs from both a health care sector and modified societal perspective. The base-case results for incremental cost-effectiveness ratios comparing deflazacort to prednisone were substantially higher than commonly used thresholds of $50,000 to $150,000 per QALY gained.

Table 4.9. Base-Case Results from Health Care Sector Perspective for Prednisone with Supportive Care and Deflazacort with Supportive Care

Treatment	Drug Cost	Total Cost	QALYs	LYs	Years in Ambulation
Prednisone + Supportive Care	$2,400	$464,000	6.88	15.05	7.97
Deflazacort + Supportive Care	$525,000	$1,010,000	8.40	16.64	10.16
Incremental	$523,000	$548,000	1.52	1.59	2.20

LY: life year, QALY: quality adjusted life year

Table 4.10. Base-Case Results from the Modified Societal Perspective for Prednisone with Supportive Care and Deflazacort with Supportive Care

Treatment	Drug Cost	Total Cost	QALYs	LYs	Years in Ambulation
Prednisone + Supportive Care	$2,400	$1,240,000	6.88	15.05	7.97
Deflazacort + Supportive Care	$525,000	$1,830,000	8.40	16.64	10.16
Incremental	$523,000	$591,000	1.52	1.59	2.20

LY: life year, QALY: quality adjusted life year

Table 4.11. Base-Case Incremental Cost-Effectiveness Ratios for Deflazacort with Supportive Care Compared to Prednisone with Supportive Care

Treatment	Cost per QALY Gained	Cost per LY Gained	Cost per Additional Year in Ambulation
Deflazacort Compared to Prednisone - Health Sector Perspective	$361,000	$343,000	$250,000
Deflazacort Compared to Prednisone - Modified Societal Perspective	$390,000	$371,000	$269,000

LY: life year, QALY: quality adjusted life year

The incremental cost-effectiveness ratios in the modified societal perspective are slightly higher (less favorable) because they include broader societal perspective costs of supportive care such as informal care and indirect cost of the illness during the increased years of ambulation for deflazacort. The differences in the modified societal perspective costs across the health states relative to the differences in the health sector perspective costs across the health states generate

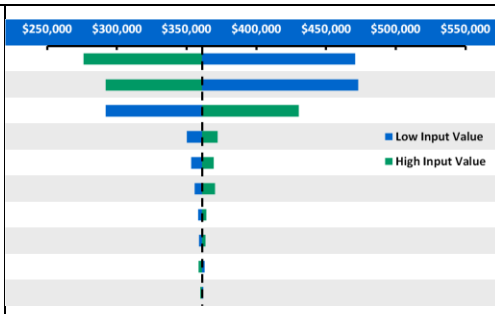
this result. In addition, to explore the impacts of added societal benefits to go along with the added societal perspective costs, caregiver QALYs are incorporated in scenario analyses below.

In this version of the report, all reported incremental results for deflazacort are substantially lower (more favorable) compared to the previously posted draft report. This is due to factors that included errors that were noted and updated, as well as a change in the model structure increasing from three to five health states. The first error that was noted was that the utility value (0.38) for the non-ambulatory health state in the draft report was much higher than the corrected values (0.21 for early non-ambulatory and 0.18 for late non-ambulatory) used in the current version of report. With the favorable treatment effect shift of three years for all subsequent health states applied to deflazacort, this was the main driver contributing to these differences in the incremental cost-effectiveness ratios. We also noted an error in the cost calculations related to dosing of deflazacort and prednisone. In the draft evidence report, we incorrectly used the prevalent doses (0.695 mg/kg/day for deflazacort and 0.515 mg/kg/day for prednisone) in the model despite having reported the package insert doses. The model was then updated to incorporate the following doses: 0.9 mg/kg/day for deflazacort and 0.75 mg/kg/day for prednisone, both of which are based on the package insert information of these drugs.

Sensitivity Analysis Results

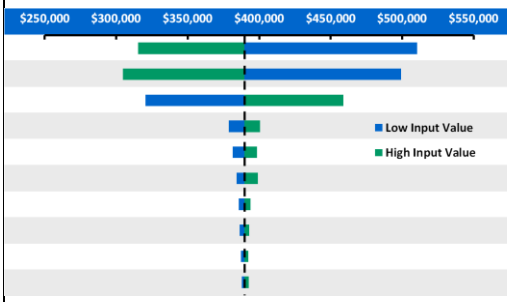
To examine effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for key drivers of variability and uncertainty. Inputs that were varied in one-way sensitivity analyses included the treatment effect shift (rightward shift of both ambulatory and mortality curves) for deflazacort, drug cost, patient utilities, discontinuation of steroids in non-ambulation, direct medical costs, weight gain, and weight gain disutility. See Figure 4.2 below for tornado diagrams with corresponding tables of high and low input values from the health care sector and modified societal perspectives. These deterministic analyses show that the treatment effect, the patient utility in the early ambulatory state, and the drug cost of deflazacort are the inputs with the most sensitivity in the model. However, even broad changes of these inputs result in incremental cost-effectiveness ratios above standard thresholds.

Figure 4.2. Tornado Diagrams for One-Way Sensitivity Analyses of Inputs on the Base-Case Incremental Cost-Effectiveness Ratio of Deflazacort versus Prednisone



Health Sector Perspective

Parameter	Low Input Value	High Input Value
Treatment Shift (Deflazacort)	1	5
Early Ambulation Patient Utility	0.58	0.88
Deflazacort Drug Cost ($/mg)	$4.95	$7.43
Deflazacort Discontinuation	0.31	0.47
Late Ambulation Patient Utility	0.51	0.77
Early Ambulatory Direct Medical (Non-Medication) Costs	$15,206	$24,300
Late Non-Ambulation Patient Utility	0.14	0.22
Early Non-Ambulation Patient Utility	0.17	0.25
Late Non-Ambulatory Direct Medical (Non-Medication) Costs	$29,849	$47,702
Early Non-Ambulatory Direct Medical (Non-Medication) Costs	$22,286	$35,616



Societal Perspective

Parameter	Low Input Value	High Input Value
Early Ambulation Patient Utility	0.58	0.88
Treatment Shift (Deflazacort)	1	5
Deflazacort Drug Cost ($/mg)	$4.95	$7.43
Deflazacort Discontinuation	0.31	0.47
Late Ambulation Patient Utility	0.51	0.77
Early Ambulatory Direct Medical (Non-Medication) Costs	$15,206	$24,300
Early Ambulatory Indirect Cost of Illness Costs	$14,790	$19,773
Late Non-Ambulation Patient Utility	0.14	0.22
Early Non-Ambulation Patient Utility	0.17	0.25
Early Ambulatory Non-Medical Community Services Costs	$4,823	$7,831

All of the parameters except for the treatment shift, which was already an upper bound estimate, were also varied in the probabilistic sensitivity analysis (see Appendix E for more detail). The results from the probabilistic sensitivity analysis of 10,000 simulations of the base-case model for deflazacort and supportive care versus prednisone and supportive care are presented below in Table 4.12(see Appendix E for more detail). 99.97% of the 10,000 simulations produced incremental cost per QALY results for deflazacort that exceeded thresholds of $150,000 per QALY. In other words, at a $150,000 per QALY threshold, deflazacort had less than a 1% probability of being cost-effective (see table below). Even at $300,000 per QALY, deflazacort is cost effective in less than 23% of the simulations. Overall, the results of the probabilistic sensitivity analysis, particularly viewed in light of the intentionally favorable assumptions to deflazacort in the model (i.e., a three-year shift in all survival curves based on observational evidence rather than the use of RCT evidence that did not show delayed disease progression), suggest that it is extremely likely that the true incremental cost-effectiveness ratio of deflazacort is well above $150,000 per QALY and very likely to be above $300,000 per QALY.

Table 4.12. Probabilistic Sensitivity Analysis Results: Proportion of Simulations of Incremental Ratios of Deflazacort Compared to Specific Willingness-to-Pay Thresholds

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $300,000 per QALY	Cost-Effective at $500,000 per QALY
Deflazacort	0.00%	0.00%	0.03%	22.47%	91.77%

QALY: quality adjusted life year

Scenario Analyses Results

The results from the scenarios in the base-case model are summarized below (see Table 4.13). If deflazacort shifted both curves by three years and eliminated the late ambulatory health state and, more importantly, the late non-ambulatory health state, it reached an incremental ratio of $290,000 per QALY gained (Scenario 2). This scenario was extremely favorable to deflazacort, as the early ambulatory and early non-ambulatory utility values, which are higher than the weighted average used in the base case, are applied to the ambulatory and non-ambulatory health state for deflazacort only. More importantly, deflazacort is also associated with large, likely implausible, cost reductions in the non-ambulatory health state in this scenario. Also, in the scenarios with one or two caregivers receiving QALY gains from the treatment that are added to the patient QALY gains, deflazacort had substantially lower (more favorable) cost-effectiveness ratios. When the QALY gains for two caregivers are included, the incremental cost-effectiveness ratio falls below $150,000.

Scenarios that stopped the base-case model after 45 cycles showed essentially identical results (given standard rounding) to those run over a lifetime using the survival curves, which indicates that potential errors in the tails of the survival curves in the model are not impacting the results.

Table 4.13. Scenario Analyses Results: Deflazacort versus Prednisone

Scenario	Treatment	Total Cost	QALYs	LYs	Incremental Cost per QALY
Scenario 1	Low dose: prednisone	$463,000	6.88	15.05	--
	Low dose: deflazacort	$892,000	8.40	16.64	$283,000
Scenario 2	Base-case value: prednisone	$464,000	6.88	15.05	--
	Early ambulatory and non-ambulatory values: deflazacort	$1,010,000	8.77	16.64	$290,000
Scenario 3	Societal perspective, 1 caregiver: prednisone	$1,240,000	19.30	15.05	--
	Societal perspective, 1 caregiver: deflazacort	$1,830,000	22.23	16.64	$202,000
Scenario 4	Societal perspective, 2 caregivers: prednisone	$1,240,000	31.72	15.05	--
	Societal perspective, 2 caregivers: deflazacort	$1,830,000	36.06	16.64	$136,000

LY: life year, QALY: quality adjusted life year

Threshold Analyses Results

Deflazacort

The results of the first threshold analysis are reported below (Tables 4.14 and 4.15) as prices per mg and corresponding annual costs for a 40-kg patient for deflazacort to reach specified willingness-to-pay thresholds when compared to prednisone. The cost of deflazacort would have to be lower than its current net price to achieve cost effectiveness at thresholds of up to $300,000 per QALY gained.

Table 4.14. Threshold Analysis 1a: Prices for Deflazacort to Meet Specific Willingness-to-Pay Thresholds per QALY Gained

	Base-Case Cost	Price to achieve $50,000 per QALY	Price to achieve $100,000 per QALY	Price achieve $150,000 per QALY	Price to achieve $300,000 per QALY	Price to achieve $500,000 per QALY
Deflazacort (Per Unit)	$6.19/mg	$0.62/mg	$1.52/mg	$2.41/mg	$5.09/mg	$8.67/ mg
Deflazacort (Per Year)	$81,400/ year*	$8,200/ year*	$19,900/ year*	$31,700/ year*	$67,000/ year*	$114,000/ year*

mg: milligram, QALY: quality adjusted life year

*Price per year is for a 40 kg patient.

Table 4.15. Threshold Analysis 1b: Prices for Deflazacort to Meet Specific Willingness-to-Pay Thresholds per LY Gained

	Base-Case Cost	Price to achieve $50,000 per LY Gained	Price to achieve $100,000 per LY Gained	Price achieve $150,000 per LY Gained	Price to achieve $300,000 per LY Gained	Price to achieve $500,000 per LY Gained
Deflazacort (Per Unit)	$6.19/mg	$0.67/mg	$1.61/mg	$2.55/mg	$5.36/mg	$9.12/mg
Deflazacort (Per Year)	$81,400/ year*	$8,800/ year*	$21,100/ year*	$33,500/ year*	$70,500/ year*	$119,900/year*

mg: milligram, LY: life year

*Price per year is for a 40 kg patient.

Eteplirsen

The second and third threshold analyses are summarized in Table 4.16. In the absence of clinical evidence of benefit with eteplirsen, these look at how very large improvements in outcomes would affect the cost effectiveness of eteplirsen at its current price. The reason that eteplirsen has such extremely high incremental cost-effectiveness ratios is that it is associated with very high annual costs throughout a patient's life. Hence, even under the most extreme and unrealistic assumption about benefits (restoring both the patient and two caregivers to perfect health for the patient's lifetime), the incremental cost-effectiveness ratio remained above $450,000 per QALY. As noted earlier, if golodirsen had the same costs as eteplirsen, these same results would hold.

Table 4.16. Threshold Analyses 2 and 3: Varying Treatment Effects of Eteplirsen as an Add-On Therapy to Prednisone and Supportive Care

Scenario	Treatment	Incremental Costs	Incremental QALYs Gained	Incremental LYs Gained	Cost per QALY	Cost per LY Gained
10 Year Shift*	Eteplirsen	$12,670,000	4.70	5.15	$2,700,000	$2,460,000
10 Year Shift Societal*	Eteplirsen	$12,820,000	4.70	5.15	$2,730,000	$2,490,000
20 Year Shift*	Eteplirsen	$17,510,000	8.20	8.63	$2,140,000	$2,030,000
20 Year Shift Societal*	Eteplirsen	$17,740,000	8.20	8.63	$2,170,000	$2,060,000
40 Year Shift*	Eteplirsen	$24,010,000	12.42	12.95	$1,930,000	$1,860,000
40 Year Shift Societal*	Eteplirsen	$24,350,000	12.42	12.95	$1,960,000	$1,880,000
40 Year Shift and Restore to Perfect Health*	Eteplirsen	$23,350,000	28.00	16.07	$1,110,000	$1,450,000
40 Year Shift and Restore to Perfect Health Societal†	Eteplirsen	$22,570,000	49.15	16.07	$459,000	$1,400,000

LY: life year, QALY: quality adjusted life year

*Scenario 2.

†Scenario 3. The much larger QALY difference is observed because the treatment is assumed to restore patients and caregivers to perfect health.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report and with supplemental Appendix materials. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

After reviewing the DMD literature, we identified two studies describing models developed for patients with DMD. Note that the below text focuses primarily on methods, not results, as the interventions used in the below models differ from those in the ICER analyses.

Landfeldt et al.[36] developed a *de novo* cost-effectiveness model using Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool (DMDSAT), a rating scale developed to measure DMD disease progression in clinical practice and trials, and compared it with two other potential model structures that were based on more conventional ambulatory or ventilatory stages. The authors evaluated a hypothetical treatment that slowed disease progression by 25% and cost $130,000 per year and compared it to best supportive care. The models used an annual cycle length over a lifetime time horizon and 3.5% discount rates for both costs and benefits. In all three models, patient utilities were derived using the HUI Mark 3 multi-attribute health status classification system, based on preference data collected from 256 randomly selected members of the general population in Hamilton, Ontario, Canada.[131]

The first model (Model I, the proposed *de novo* model) included 25 health states, one for each DMDSAT score and death, where they assumed a linear disease progression associated with DMDSAT score and two steps of health decline per year. Furthermore, given that the proposed model structure was limited by the lack of longitudinal natural history data linked to the DMDSAT scale, it requires further investigation and validation. The second model (Model II, which was the most similar to the ICER model in terms of model structure), included five states: early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory, and death, where they assumed a linear disease progression based on age in ambulatory health states, which was then continued for subsequent health states. In Model II, the utility value in the ambulatory stage after applying the proportions of patients in early and late ambulatory stages used in this review was close to that used in ICER model (0.64 vs 0.61, respectively). Based on the wide range we used in our one-way sensitivity analysis (0.56-0.74), that difference in utility values would not substantially impact our conclusions. The utility value in the non-ambulatory health state was relatively lower than the one in ICER model (0.18 vs 0.31, respectively); because the utility in non-ambulatory health state had a very minor impact on the cost per QALY results in this review, we do not anticipate that it would influentially change the model outcomes. The third model (Model III) included four states: no ventilation support, night-time ventilation support, day- and night-time ventilation support, and death, where the progression of the disease was estimated based on the time to ventilation support. The authors found that the incremental cost-effectiveness ratios were $1,443000 (Model I), $1,940,000 (Model II), and $3,575,000 (Model III) per QALY gained in 2017 US dollars from a health care perspective. Based on these results, the authors concluded that as the model became more granular, it was more likely to have more favorable incremental cost-effectiveness ratios. However, this result depended heavily on the underlying treatment effect for the hypothetical treatment. ICER conducted multiple scenario analyses that were even more highly favorable to deflazacort, and only the final one of these extremely favorable analyses (the scenario that added QALY gains for two caregivers to the patient gains) produced an incremental cost-effectiveness ratio below $150,000 per QALY gained for deflazacort. Similarly, only our final scenario analysis for eteplirsen produced an incremental cost-effectiveness ratio below $500,000/QALY gained. Also, as

noted above, the health states and utility values used by Landfeldt et al.[36] were based on assumptions (i.e., not derived from trial data or health state utilities from DMD patients or caregivers). We did not take a similar approach because there was no quality of life data from DMD patients or caregivers to inform additional health states and, further, no evidence on how deflazacort or eteplirsen would impact transitions between these states.

In the NICE review[38] of a submission by PTC Therapeutics, the cost effectiveness of ataluren compared to best supportive care was evaluated. The company submitted three models. The health states in the all three models were similar to those used in the ICER model, and were ambulatory, non-ambulatory, non-ambulatory with ventilation-assistance, non-ambulatory with scoliosis, non-ambulatory with ventilation-assistance and scoliosis, and death. The utility values in the models were informed by Landfeldt et al.,[10] as in the ICER model. The first and third models used discount rates of 3.5% whereas the second one used 1.5% discount rate; these rates were applied to both costs and benefits in their respective models. All three models used a three-month cycle length. In the first model, the time horizon of the model was limited to the last point when at least one patient was in the ambulatory state (because only patients who could walk had treatment). In the second and third models, a lifetime time horizon was adopted.

The first model resulted with an incremental cost-effectiveness ratio of $2,384,000 in 2008 US dollars. This version was mainly criticized for not having additional treatment costs, applying treatment only in the ambulatory stage, and using the same treatment benefit for ataluren over time (i.e., linear extrapolation). After resolving the concerns raised in the first model, the company submitted a second model in which they also updated the following assumptions: 1) a lower discount rate, 2) updated parametric curves used to estimate the time to scoliosis, ventilation assistance, and death, and 3) patients who were ambulatory did not die from DMD-associated causes, which could result in more favorable cost-effectiveness findings. These changes in the second model produced an incremental cost-effectiveness ratio of $1,323,000. NICE expressed concerns with the method used to extrapolate 6MWT and considered the linear extrapolation method to be inappropriate. The company developed its third model based on feedback from the evidence review group on its two prior submissions. Base-case results of this final model were confidential and therefore not published in the submission document.

Limitations

DMD is an ultra-rare disease and there were insufficient clinical trial data for modeling treatment effects for eteplirsen or golodirsen. Existing available information for this patient population also precluded detailed modeling of how the disease progresses beyond the five states we employed. Further, head-to-head evidence for the effect of deflazacort versus prednisone was also limited and mixed. We used evidence for a treatment effect of deflazacort relative to prednisone from a selected cohort study that was among the largest available treatment effects seen in the literature

for deflazacort. This was a very conservative approach to favor deflazacort as several RCTs comparing the two corticosteroids found no statistically significant difference in effectiveness.[20,21,106] In addition, several of the model inputs came from cohort studies that could have been subject to selection bias. However, we performed several sensitivity and scenario analyses and our findings suggest that the basic conclusions of the analyses were robust to substantial potential variance in the inputs.

Also, available cost and utility estimates related to measurable health states in DMD were essentially limited to the health states of early and late ambulation and early and late non-ambulation. While these provided reasonable first-order estimates of health gains associated with extended time before loss of ambulation and with potential reductions in mortality, treatments that impact the relative quality of life in a more granular model of the disease progression may have different health effects than those projected here. Our model only comprised five health states and there may be important treatment benefits that could not be captured here. This lack of granularity was due to a lack of evidence on how the available treatments might impact additional health states. We used parallel shifts in all the curves as we could not identify any evidence of treatment effects impacting the relative time spent in early versus late stages.[36,38] Nonetheless, we used highly favorable treatment effects and assumptions and the sensitivity and scenario analyses indicated that the conclusions regarding the cost effectiveness of these treatments were highly robust. If treatments extend time in early non-ambulation relative to late non-ambulation, that would tend to make them more cost-effective, but given the already highly favorable treatment effects used here, treatment effects that may present themselves in future data will almost certainly be associated with incremental cost-effectiveness ratios above estimates for commonly used thresholds.

Existing projections for treatment outcomes are for all DMD patients and are based in part on international data where there may be differences from US patients. Also, patients eligible for eteplirsen and golodirsen may have different characteristics and outcomes than those of other DMD patients that may not be reflected in the base-case comparator. However, as demonstrated by our extensive scenario/sensitivity analyses, our conclusions were extremely robust at the current treatment prices. Finally, it is a known limitation of estimating survival curves that the tails may be too “fat”, and this appears to be the case in the curves we adopted. The tails become fat when the curves asymptote at y=0 (corresponding with patient age in our model), when in reality we know all patients should exit the model by a certain age. In particular, patients in the model may be more likely to be in the non-ambulatory state versus dead at ages greater than 50. Again, though, scenario analyses that stopped the model after 45 cycles indicated that any potential bias in the tails of the curves is minor and did not impact our results.

Conclusions

The underlying evidence for evaluating the cost effectiveness of treatments in DMD remains sparse. Nonetheless, based on available information regarding treatment costs and underlying health states associated with DMD, when compared to prednisone, deflazacort is projected to have very high costs relative to its benefits for patients and families. For eteplirsen, at its current price, no plausible treatment effects were found to make this treatment reach cost-effectiveness thresholds below $150,000 per QALY gained and only one curative scenario resulted cost effectiveness below a $500,000 per QALY threshold. Similar results are expected of golodirsen if it is priced similar to eteplirsen.

4.4 Summary and Comment

Available evidence on the costs and utilities in health states associated with DMD were synthesized to allow estimation of the cost effectiveness of deflazacort as well as to consider threshold effects (QALYs required), given costs, for eteplirsen. Specifically, deflazacort and best supportive care were examined relative to prednisone and best supportive care. In addition, eteplirsen and golodirsen were considered as add-on therapy to corticosteroids and best supportive care. Since there was insufficient evidence of a treatment effect for eteplirsen, only threshold analyses were reported. For golodirsen there was neither treatment effect nor pricing information available. However, if golodirsen costs the same as eteplirsen, the threshold analyses for eteplirsen would directly apply.

For deflazacort, our base-case analyses showed incremental cost-utility ratios exceeding the $150,000 per QALY willingness-to-pay threshold even with favorable assumptions regarding treatment effects. The deterministic and probabilistic sensitivity analyses further supported this finding.

For eteplirsen, at its current price, threshold analyses suggested that it would not be cost-effective at a willingness-to-pay threshold of $150,000 per QALY even with assuming extremely favorable treatment effects that are not credible given clinical evidence. Again, by extension, the same results would apply to golodirsen if it is priced similarly to eteplirsen.

While there are important limitations to consider, which are delineated below, the magnitudes of the treatment costs relative to the potential health effects projected for DMD suggest serious concerns regarding the cost-effectiveness of these treatments at current prices. A broad set of threshold and scenario analyses suggest these concerns are robust to a wide set of potential variances in actual treatment effects and demonstrate that at current prices, the treatment effects would have to be substantial and beyond any current projections from available evidence for the treatments to be cost-effective at currently accepted willingness-to-pay thresholds.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of deflazacort and prednisone, and exon-skipping therapies in addition to corticosteroids and supportive therapy. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's Value Assessment Framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

Based on ICER's adaptation of the value framework for rare diseases, treatments for DMD may have a number of potential other benefits.

- DMD is a progressive muscle wasting disease, and supportive care, particularly towards the end of life, can involve very extensive interventions such as assisted ventilation, scoliosis surgery, and therapy for heart failure. Therapies that may delay or prevent the muscle decline, scoliosis, or respiratory or cardiac compromise, may improve quality and duration of life for patients, decrease caregiver burden, and lead to the ability for patients and caregivers to be more productive in terms of school and work.
- Exon-skipping therapies represent a novel mechanism of action for treating DMD.

5.2 Contextual Considerations

There are a number of contextual considerations relevant to treatment of DMD patients.

- DMD is a severe and fatal disease, and due to complications of the disease including loss of ambulation, scoliosis, and respiratory and cardiac compromise, as well as treatment side effects such as osteoporotic fractures and weight gain, the impact of the disease on patients and caregivers is substantial.
- Due to the fact that DMD is an ultra-rare disease, conducting rigorous clinical trials of sufficient duration to demonstrate clinical efficacy and gather adequate safety data is challenging. Surrogate endpoints and use of historical controls have allowed for some preliminary assessments of efficacy and safety, particularly for exon-skipping drugs; however, findings must be verified in future studies.
- Due to differences in trial populations, dosing, outcome measurements, and study duration, as well as a lack of long-term randomized, controlled trial data, there is uncertainty about the differences in long-term efficacy and serious side effects of deflazacort compared with prednisone.
- Due to the fact that exon-skipping drugs were approved through the FDA's accelerated approval pathway, drugs for serious conditions that meet an unrealized medical need are approved on the basis of whether the drug has an effect on an intermediate or surrogate clinical endpoint[132]; the clinical efficacy of these drugs is unknown. Furthermore, there is a lack of long-term data for exon-skipping therapies and thus the potential long-term benefits and harms of these drugs is unknown, particularly in comparison to supportive care and corticosteroids.
- Current outcome measures may not adequately capture the clinical effects of treatment.

6. Value-Based Price Benchmarks

Annual value-based price benchmarks (VBPBs) of deflazacort for the treatment of DMD patients are presented in Table 6.1. As noted in the ICER Value Assessment Framework Modifications for Ultra-Rare Diseases, the VBPB for a therapy is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

As discussed above, the model made assumptions from observational data that are likely very favorable to deflazacort, and so these VBPBs should be considered as upper limits on appropriate value-based prices. If the model had used estimates from randomized trial data, the VBPBs would be much lower. For deflazacort, under these favorable assumptions, price discounts of approximately 73% to 83% from the list price (WAC) would be required to reach the $150,000 to $100,000 per QALY threshold prices, respectively. Similar price discounts of approximately 71% to 82% from the list price (WAC) would be required to reach the $150,000 to $100,000 per LY gained threshold prices, respectively (Table 6.1).

Table 6.1. Value-Based Price Benchmark for Deflazacort Using Favorable Assumptions

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Per QALY Gained	$117,400	$19,900	$31,700	73% to 83%
Per LY Gained		$21,100	$33,500	71% to 82%

WAC: wholesale acquisition cost; QALY: quality-adjusted life year; LY: life year

*Price per year is for a 40 kg patient.

VBPBs could not be calculated for eteplirsen or golodirsen in the absence of evidence demonstrating clinical benefits.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of deflazacort in patients with DMD in the US. We used deflazacort's list price ($117,400/year), the net price ($81,400/year), and the three threshold prices to achieve cost effectiveness at $50,000, $100,000, and $150,000 per QALY ($31,700/year, $19,900/year, and $8,200/year, respectively) in our estimates of budget impact. We did not conduct cost-effectiveness analyses in the base case for eteplirsen or golodirsen because there was insufficient evidence to model treatment effects. Therefore, we did not have the cost data needed to estimate the potential budget impact of eteplirsen and golodirsen.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was of interest given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate population eligible for treatment—patients in the US diagnosed with DMD who are five years of age or older. To estimate the size of the potential candidate population for deflazacort, we used the point prevalence for DMD (0.4 per 10,000 males)[43] and applied it to the projected 2019 to 2023 target male population in the US to derive the average number of DMD patients in the next five years. This resulted in an estimate of approximately 6,200 people with DMD in the US. We assumed an equal proportion of patients would be treated each year over five years, or approximately 1,240 patients per year. In the absence of indications to the contrary, we assumed that all patients diagnosed with DMD would be eligible for treatment with deflazacort.

ICER's methods for estimating potential budget impact are described in detail elsewhere[133] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we evaluated the potential budget impact of using deflazacort compared to prednisone and supportive care for DMD treatment.

7.3 Results

Table 7.1 illustrates the per-patient budget impact calculations in more detail, based on the list price, the net price, and the prices to reach $150,000, $100,000, and $50,000 per QALY for deflazacort compared to prednisone.

Table 7.1. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per-Patient Budget Impact				
	At List Price	At Net Price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Deflazacort (Annualized Cost)	$83,200	$68,800	$38,900	$32,900	$26,800
Prednisone (Annualized Cost)	$22,900				
Deflazacort Budget Impact*	$60,300	$45,900	$16,000	$10,000	$3,900

QALY: quality-adjusted life year

*Difference between deflazacort and prednisone costs

The average annual potential budgetary impact when using the list price was an additional per-patient cost of approximately $60,300, and approximately $46,000 when using the net price. Average annual potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $16,000 per patient using the price per dose to achieve $150,000 per QALY to approximately $3,900 using the price per dose to achieve a $50,000 per QALY threshold.

For deflazacort, the annual potential budgetary impact of treating the entire eligible population across all prices (list price, net price, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) did not exceed the $819 million threshold, due to the relatively small number of patients eligible for treatment each year. Overall, the potential budget impact of deflazacort treatment reached 23% of the threshold using the list price, and 18% of the threshold with the net price. For the three cost-effectiveness threshold prices at $150,000, $100,000, and $50,000 per QALY, the potential budget impact reached only approximately 6%, 4% and 2% of the threshold, respectively.

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This is the first ICER review of treatments for Duchenne muscular dystrophy.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

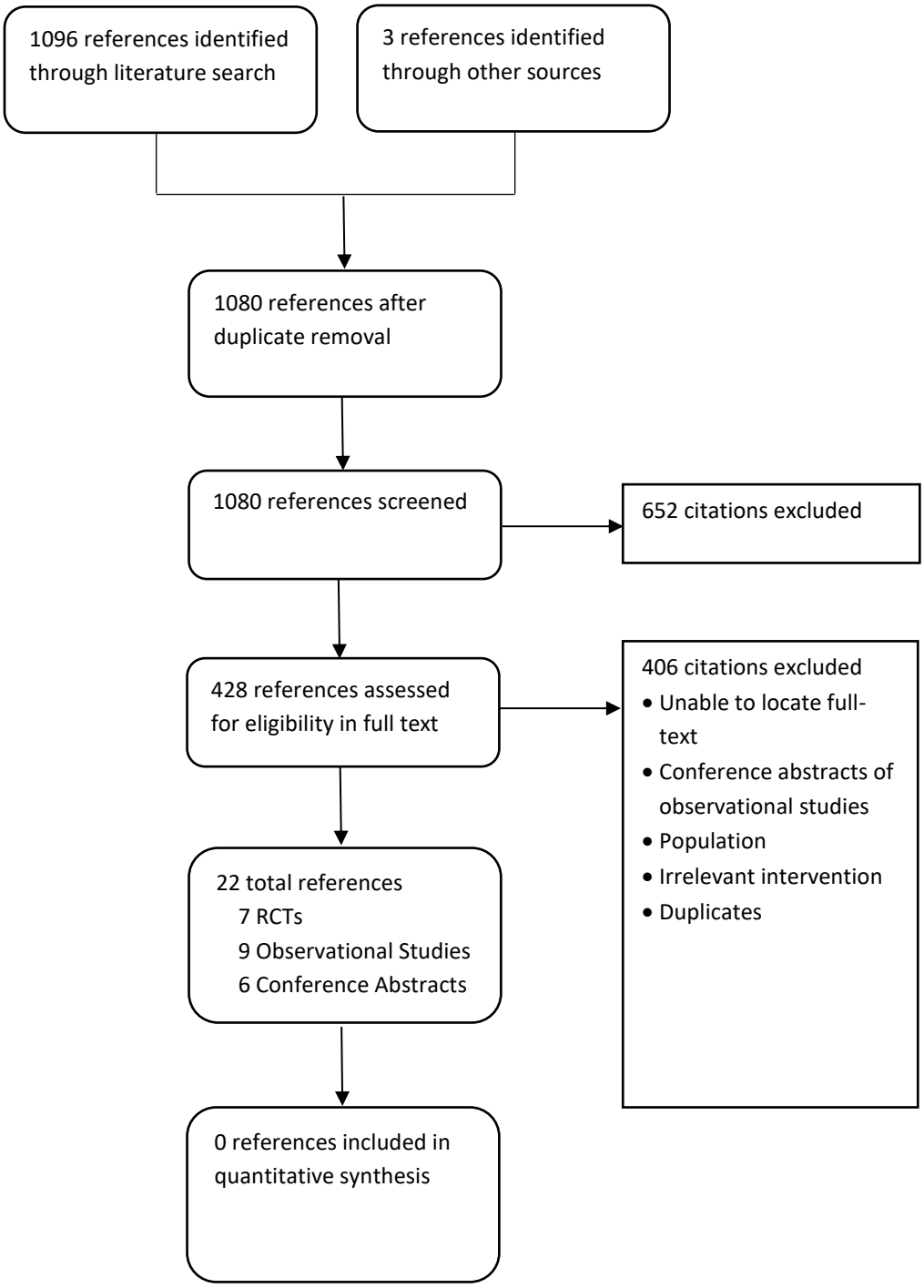
Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials via Ovid, March 19, 2019.

#	Search Terms
1	exp Duchenne muscular dystrophy/
2	(Duchenne muscular dystrophy or DMD).mp.
3	Exon skipping.mp.
4	OR/1-3
5	(eteplirsen OR exondys#?51 OR avi#?4658).mp.
6	(golodirsen OR srp#?4053).mp.
7	(deflazacort OR emflaza OR zamen* OR calcort OR dezacor OR cortax OR decortil OR deflanil OR MOAID OR xalcort).mp.
8	exp steroids/ OR exp glucocorticoids/
9	(steroid* OR corticosteroid* OR glucocorticoid*).mp.
10	exp prednisone/
11	(predniso* OR deltason* OR rayor OR delta-cortef OR meticorten OR orason*).mp.
12	OR/5-11
13	4 AND 12
14	(animals not (humans and animals)).sh.
15	13 NOT 14
16	(addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development OR conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt.
17	15 NOT 16
18	limit 17 to English language
19	remove duplicates from 18

Table A3. Embase Search Strategy, March 19, 2019.

#	Search Terms
#1	'Duchenne muscular dystrophy'/exp
#2	'DMD protein human'
#3	#1 OR #2
#4	'eteplirsen'/exp OR 'golodirsen'/exp OR 'deflazacort'/exp
#5	eteplirsen:ti,ab OR exondys*51:ti,ab OR avi*4658:ti,ab
#6	golodirsen:ti,ab OR srp*4053:ti,ab
#7	(deflazacort OR emflaza OR zamen* OR calcort OR dezacor OR cortax OR decortil OR deflanil OR MOAID OR xalcort):ti,ab
#8	#4 OR #5 OR #6 OR #7
#9	'prednisone' OR 'prednisolone' OR 'steroid' OR 'corticosteroid' OR 'glucocorticoid'
#10	predniso*:ti,ab OR deltason*:ti,ab OR rayor:ti,ab OR delta-cortef:ti,ab OR meticorten:ti,ab OR orason*:ti,ab
#11	#9 OR #10
#12	#3 AND (#8 OR #11)
#13	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#14	#12 NOT #13
#15	#14 AND [english]/lim
#16	#14 AND [medline]/lim
#17	#15 NOT #16
#18	#17 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#119	#17 NOT #18

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Duchenne Muscular Dystrophy



Appendix B. Previous Systematic Reviews and Technology Assessments

Campbell C, Jacob P. Deflazacort for the treatment of Duchenne Dystrophy: A systematic review. *BMC Neurology*. 2003; 3(7).

The investigators evaluated the clinical effectiveness and safety of deflazacort for Duchenne Muscular Dystrophy (DMD). Five studies (two placebo-controlled trials, two head-to-head trials versus prednisone, and one study included both placebo and prednisone comparison) were included into the review. Efficacy endpoints across the studies were categorized into strength measurements, functional measures, and time to loss of ambulation. Evidence suggests a clinically meaningful and statistically significant benefit of deflazacort on strength measurements in comparison to no treatment (placebo). Compared to prednisone however, the authors concluded the two treatments to be comparable in efficacy. Weight gain was the most commonly reported side effect across studies, while deflazacort lead to less severe weight gain compared to prednisone. Conclusions regarding other adverse events could not be made due to irregularities in reporting. The authors noted that the current evidence is lacking and pointed out the need for additional, high quality data to better compare the clinical efficacy of deflazacort and prednisone.

Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database of Systematic Reviews*. 2016;5.

The objective of this review was to assess the treatment effects of corticosteroids on delaying loss of ambulation, muscle strength, functional ability, and quality of life in boys with DMD. Twelve studies and two ongoing trials were included in this review. Of the 14 studies included, seven were quantitatively analyzed. Nine trials compared steroid treatment to placebo, one trial compared daily to weekend-only prednisone, and three trials compared deflazacort to prednisone. Only one placebo-controlled trial of deflazacort assessed ambulation. Meta-analyses showed that at six months, 0.75 mg/kg/day prednisone was efficacious in improving muscle strength, as well as muscle and pulmonary function when compared to placebo. One RCT showed benefit for deflazacort versus placebo in muscle strength. Differences in trial methodology did not allow for an adequate comparison of muscle strength or function for deflazacort versus prednisone. Safety assessments showed excessive weight gain, abnormal behavior, changes in appearance, and abnormal hair growth to be more common in boys treated with steroids when compared to placebo. Two low quality studies indicated that deflazacort appeared to cause less severe weight gain at 12 months compared to prednisone. Findings from non-randomized studies were generally similar. The authors noted the lack of long-term data as a major limitation of this review.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Deflazacort					
Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) NCT01603407 **Phase 3** **University of Rochester**	Randomized, quadruple-blinded, parallel-assignment trial Estimated N: 196	*(Duration: 36 – 60 months)* **Deflazacort (oral)** – 0.9mg/kg/day **Prednisone (oral)** – 0.75mg/kg/day – 0.75mg/kg/day; 10 days on and 10 days off treatment	**Inclusion** – Male, 4 – 7 years – Ability to rise independently from floor, from supine to standing **Exclusion** – History of major renal or hepatic impairment, immunosuppression, or other contraindications – History of chronic systemic fungal or viral infections; acute bacterial infection (incl. TB) – Diabetes mellitus – Idiopathic hypercalciuria – Lack of chicken pox immunity/ refusal to undergo immunization – Evidence of symptomatic cardiomyopathy – Current or previous treatment with corticosteroids or other immunosuppressive – Inability to take tablets – Allergy/sensitivity to study drugs or their formulations – Severe behavioral problems – Weight of less than 13 kg – Exposure to any investigational drug currently or within 3 months prior	**Primary Outcomes** *[Measured at months 3, 6, 12, 18, 24, 30, and 36]* – Three-dimensional multivariate outcome (time to stand from supine, FVC, subject/parent global satisfaction with treatment) **Secondary Outcomes** *[Measured at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60]* – NSAA (also measured during screening and at baseline) – 6MWT (also measured during screening and at baseline) – Range of motion (also measured during screening and at baseline) – Regimen tolerance – Incidence of AEs – Quality of Life (also measured at baseline) – Cardiac function (measured during screening, then every two years to the age of 10, and annually thereafter or at the onset of cardiac symptoms)	October 2019
Eteplirsen					
Study of Eteplirsen in DMD Patients (PROMOVI)	Open-label, non-	**Eteplirsen (IV)** – Weekly 30 mg/kg/week	**Inclusion Criteria** – Male, 7-16 years old	*[Time Frame: Change from Baseline to Week 96]*	May 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Phase 3 NCT02255552 **Sarepta Therapeutics**	randomized, parallel assignment, multicenter trial Estimated N: 110	for 96 weeks followed by a safety extension (≤ 48 weeks) **No intervention** – Patients not amenable to exon 51 skipping will not receive eteplirsen	– Diagnosed with DMD, genotypically confirmed – Stable dose of corticosteroids for at least 24 weeks – Have intact right and left alternative upper muscle groups – Mean 6MWT greater than 300 meters – Stable pulmonary and cardiac function **Exclusion Criteria** – Previous treatment with any antisense agent or gene therapy within the 6 months prior – Participation in any other DMD interventional clinical study within 12 weeks – Major surgery within 3 months – Presence of other clinically significant illness – Major change in the physical therapy regime within 3 months	**Primary Outcome** – 6MWT distance **Secondary Outcomes** – Percentage of dystrophin-positive fibers – Maximum inspiratory/expiratory pressure percent predicted	
Study of Eteplirsen in Young Patients with DMD Amenable to Exon 51 Skipping **Phase 2** NCT03218995 **Sarepta Therapeutics**	Open-label, single group assignment, dose-escalation study Estimated N: 12	**Eteplirsen** – IV infusion* once a week for up to 96 weeks **Starting dose: 2 mg/kg (dose escalation to 4, 10, 20, and 30 mg/kg over the course of the dose-titration period)*	**Inclusion Criteria** – Male, 6 – 48 months – DMD with a deletion amenable to exon 51 skipping **Exclusion Criteria** – Received treatment that might have an effect on muscle strength or function within 12 weeks prior to dosing – Received previous or current treatment with any experimental treatment – Clinically significant illness other than DMD – Clinically significant laboratory abnormality – Any other condition that could interfere with the patient's participation	**Primary Outcomes** *[Time Frame: Up to 96 Weeks]* – Incidence of AEs: abnormal changes from baseline or clinically significant worsening of clinical safety laboratory abnormalities; vital signs; physical examination findings; ECG and ECHO **Secondary Outcomes** *[Time Frame: 24 Weeks]* – Max. plasma concentration (Cmax) – Time of Cmax (Tmax) – Area under the concentration-time curve (AUC) – Apparent volume of distribution at steady state (Vss)	August 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
				– Total clearance; urinary clearance – Elimination half-life	
Golodirsen					
Phase I/II Study of SRP-4053 in DMD Patients **Phase 1, 2** NCT02310906 **Sarepta Therapeutics**	Randomized, quadruple blinding, parallel assignment study Part 1: Randomized, placebo-controlled dose-titration Part 2: open-label evaluation Estimated N: 39	**SRP-4053** Part 1: weekly IV at escalating dose levels* for 12 weeks **Weeks 1-2, 4 mg/kg/week; Weeks 3-4, 10 mg/kg/week; Weeks 5-6, 20 mg/kg/week; Weeks 7-12, 30 mg/kg/week)* Part 2: weekly IV (30 mg/kg/week) for up to 168 weeks **Placebo** Part 1: weekly IV for 12 weeks Part 2: weekly IV assessed through week 144	**Inclusion Criteria** – Male, 6 – 15 years – Intact right and left biceps muscles or an alternative upper arm muscle group – Stable pulmonary and cardiac function – Minimum performance on 6MWT, NSAA and rise test – On stable corticosteroids dose for at least 6 months **Exclusion Criteria** – Previous treatment with BN-195 or PRO-053 – Treatment with any other experimental treatments within 12 weeks prior to study entry – Major surgery within the last 3 months – Major change in physical therapy regime within the last 3 months	**Primary Outcomes** Part 1: – Incidence of AEs and SAEs at 12 weeks Part 2: – Change from baseline in 6MWT walking distance at week 144 – Change from baseline in dystrophin levels at week 48 **Secondary Outcomes** Part 1*: [Time Frame: Pre-dose, 5 to 10 minutes, and 1 to 24 hours post-dose at weeks 1, 3, 5 and 7]* – Max. plasma concentration (Cmax) – Time to Cmax (Tmax) – Area under the plasma concentration-time Curve (AUC) – Apparent Volume of distribution at steady state (Vss) – Elimination half-life – Total clearance; urinary clearance – Mean residence time Part 2: *[Time Frame: Day 1, 0-4 hours, 4-8 hours, 8-12 hours, and 12-24 after initiation of dosing]* – Change from baseline in FVC % predicted through week 144 – Change from baseline in dystrophin intensity levels at week 48 – Measurement and sequence verification	March 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
				of Exon 53 skipped mRNA at 48 weeks	
Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE) **Phase 3** NCT02500381 **Sarepta Therapeutics**	Randomized, parallel-assignment, quadruple-blind, multicenter study Estimated N: 222 – Part 1: double-blind and randomized – Part 2: open-label extension	**SRP-4045** – Part 1: Weekly IV infusion (30 mg/kg/week for up to 96 weeks) – Part 2: Weekly IV infusion (30 mg/kg/week) for an additional 48 weeks **SRP-4053** – Part 1: Weekly IV infusion (30 mg/kg/week for up to 96 weeks) – Part 2: Weekly IV infusion (30 mg/kg/week) for an additional 48 weeks **Placebo** – Matching IV placebo	**Inclusion Criteria** – Male, 7 – 13 years – Genetic deletion amenable to exon 45 or exon 53 skipping – Stable dose of oral corticosteroids for at least 24 weeks – Mean 6MWT ≥ 300 meters and ≤ 450 meters – Stable cardiac and pulmonary function **Exclusion Criteria** – Previous treatment with SMT C1100 (BMN-195) – Treatment with gene therapy; PRO045 or PRO053 within 24 weeks prior; any other experimental treatment (other than deflazacort) within 12 weeks prior – Participation in any other DMD interventional clinical study within 12 weeks prior to Week 1 – Major surgery within 3 months prior – Major change in physical therapy regimen within 3 months prior	**Primary Outcome** – Change from Baseline in the total distance walked during 6MWT at week 96 **Secondary Outcome** – Change from baseline: total 6MWT walking distance at week 144, dystrophin protein and dystrophin intensity levels at weeks 48 or 96, NSAA total score at weeks 96 and 144, Forced Vital Capacity % predicted at weeks 96 and 144 – Ability to rise independently from the floor at weeks 96 and 144 – Time to loss of ambulation at baseline, weeks 96 and 144	May 2022
An Extension Study to Evaluate Casimersen or Golodirsen in Patients with Duchenne Muscular Dystrophy **Phase 3** NCT03532542	Open-label, non-randomized, parallel assignment, multicenter trial Estimated N: 260	**Casimersen** weekly IV infusions, 30 mg/kg for up to 144 Weeks **Golodirsen** weekly IV infusions, 30 mg/kg for up to 144 Weeks	**Inclusion Criteria** – Male, 7 – 23 years – Completed clinical trial evaluating casimersen or golodirsen – DMD amenable to exon 45 skipping or exon 53 skipping	**Primary Outcome** – Number of patients with SAEs (up to 30 days after last IV for up to 148 weeks)	June 2026

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Sarepta Therapeutics					

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

6MWT: 6-minute walk test, AEs: adverse events, DMD: Duchenne muscular dystrophy, ECG: electrocardiogram, ECHO: echocardiogram, FVC: Forced Vital Capacity, IV: intravenous, kg: kilogram, max.: maximal, mg: milligram, N: number, N: total number, NSAA: North Star Ambulatory Assessment, RNA: ribonucleic acid, SAEs: serious adverse events, TB: Tuberculosis,

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents in our review. These included the manufacturer's submission to the agency, internal FDA review documents, FDA labels, and the transcript of Advisory Committee deliberations and discussions.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[134] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

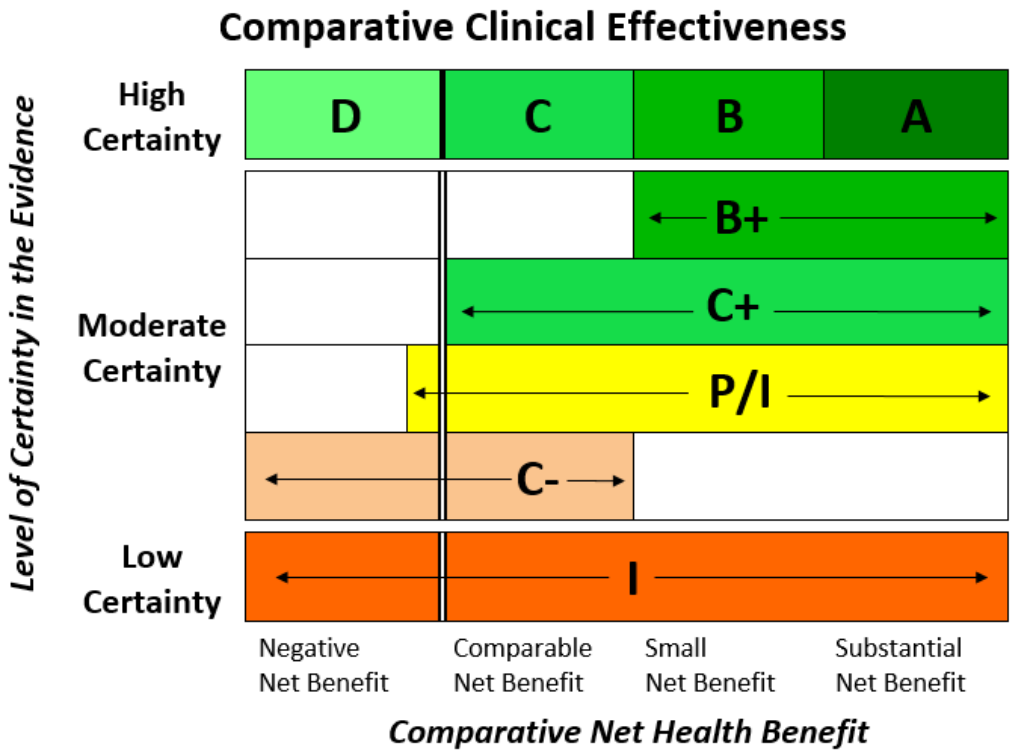
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[103]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. RCTs – Study Design

Author / Trial Name & Year of Publication Quality Rating	Study Design, Location, and Duration of Follow-up	N	Interventions (n) & Dosing Schedule	Inclusion Criteria	Exclusion Criteria
Deflazacort (DFZ) vs. Prednisone (PRED)					
Griggs, 2016[106] **Good**	Phase III, double-blind, randomized, multicenter trial US & Canada Follow-up: 52 weeks – Phase 1: 12 weeks – Phase 2: 40 weeks	196	**DFZ (oral)** – 0.9 mg/kg daily (n=51) – 1.2 mg/kg daily (n=49) **PRED (oral)** – 0.75 mg/kg daily (n=46) **Placebo (oral)** – Re-randomized to receive either daily DFZ 0.9 mg/kg, DFZ or 1.2 mg/kg, or PRED 0.75 mg/kg (oral) at 12 weeks	Male; 5-15 years; onset of weakness before 5 years old; increased serum creatine kinase activity (≥ 10x ULN); and either genetic analysis of the dystrophin gene or muscle biopsy that showed a clear alteration in dystrophin amount or distribution in the muscle	Prior steroid use (>1 year); steroid use for ≥1 month within 6 months of study or <1 month within 2 months of study; gastrointestinal issues; glycogen storage disease; dermatomyositis
Karimzadeh, 2012[20] **Poor**	Single-blind, randomized clinical trial Iran Follow-up: 18 months	26	**DFZ (oral)** – 0.9 mg/kg daily **PRED (oral)** – 0.75 mg/kg daily	Confirmed DMD diagnosis; Muscular weakness below the age of 5 years; male; an increase of more than 40-fold the normal limit of creatine kinase in the beginning of the symptoms	Uncontrollable complications (during study)
Bonifati, 2000[21] **Fair**	Double-blind, randomized, multicenter trial Italy Follow-up: 1 year	18	**DFZ (oral)** – 0.9 mg/kg daily **PRED (oral)** – 0.75 mg/kg daily	Diagnosis of DMD confirmed by dystrophin immunohistochemistry; >5 years old; preserved ability to ambulate independently; no previous steroid therapy	NR
Eteplirsen					
Study 201[29] **Fair**	Phase II-b, randomized, single-center clinical trial with open-label extension US Follow-up: 28 weeks – 24 weeks (randomized, double-blind)	12	**Eteplirsen (IV)** – 30 mg/kg/week – 50 mg/kg/week **Placebo (IV)** – Delayed eteplirsen treatment (crossover to treatment arms after 24 weeks)	Male; 7-13 years; DMD diagnosis amenable to exon 51 skipping; stable cardiac function; stable respiratory function (FVC%p≥50%); on stable dose of glucocorticoid treatment for ≥24 weeks; baseline distance in 6MWT between 200 and 400 meters	Pharmacologic treatment other than corticosteroids; previous treatment with eteplirsen, BMN-195, or PRO051; surgery within 3 months before or planned surgery during study; other comorbidities; use of aminoglycoside antibiotic within 12 weeks of screening

Author / Trial Name & Year of Publication Quality Rating	Study Design, Location, and Duration of Follow-up	N	Interventions (n) & Dosing Schedule	Inclusion Criteria	Exclusion Criteria
	– 4 weeks (open label)				
Study 202[30]	Open label, multi-dose extension trial of Study 201 US Follow-up: 4 years	12	**Eteplirsen (IV)** – 30 mg/kg/week – 50 mg/kg/week	Male; 7 – 13 years; baseline distance in 6MWT between 180 and 440 meters; stable corticosteroid therapy for ≥24 weeks; successful completion of study 201 (28 weeks)	Prior or ongoing medical condition that could adversely affect the safety of the subject or impair assessment of study results
Study 204[30,31]	Open label, multi-center, safety study US Follow-up: – 96 weeks – Up to 48 weeks safety extension	24	**Eteplirsen (IV)** – 30 mg/kg/week	Male; 7-21 years; DMD amenable to exon 51 skipping; either on stable oral glucocorticoid dose or have not received glucocorticoids for ≥24 weeks prior to study; stable cardiac and respiratory functioning; non-ambulatory or incapable of walking ≥300m on 6MWT	Pharmacologic treatment (other than corticosteroids) within 12 weeks; previous treatment with SMT C1100/BMN 195; previous treatment with drisapersen within the last 6 months; major surgery within 3 months; clinically significant comorbidity; FVC % predicted <40%; requires therapy for heart failure; LVEF of <40%
Study 301[31]	Open-label, multi-center study Follow-up:96 weeks	42	**Eteplirsen (IV)** 30 mg/kg/week **Untreated group** DMD patients not amenable to exon 51 skipping	Male; 7 – 16 years; confirmed DMD diagnosis; stable corticosteroid treatment for ≥24 weeks; 6MWT distance >300m; stable pulmonary function	Previous treatment with drisapersen or any other RNA antisense agent or any gene therapy within the last 6 months; participation in any other DMD interventional clinical study within 12 weeks; major surgery within 3 months; presence of other clinically significant illness; major change in the physical therapy regime within 3 months
Golodirsen					
Muntoni, 2018[135]	Phase I/II, randomized, double-blind, multicenter clinical trial with open-label extension International Follow-up: – Part 1: 12 weeks – Part 2: up to 168 weeks	39	**Golodirsen (IV)** – Part 1 (dose-escalation): Weeks 1-2: 4 mg/kg/wk, Weeks 3-4: 10 mg/kg/wk, Weeks 5-6: 20 mg/kg/wk, Weeks 7-12: 30 mg/kg/wk – Part 2 (open-label extension): 30 mg/kg/wk* **Placebo (**Part 1) **Untreated group** not amenable to exon 53	Males; 6 -15 years; confirmed DMD diagnosis; stable pulmonary and cardiac function; minimum performance of 250m on 6MWT; North Star Ambulatory Assessment > 17; rise (Gowers) test < 7 seconds; and on stable dose of corticosteroids for at least 6 months	Previous treatment with specific 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 regime within the last 3 months

Author / Trial Name & Year of Publication Quality Rating	Study Design, Location, and Duration of Follow-up	N	Interventions (n) & Dosing Schedule	Inclusion Criteria	Exclusion Criteria
			skipping (Part 2) **consisting of patients from Part 1 (treatment and placebo arms) & newly recruited patients*		

6MWT: 6-minute walk test, DMD: Duchenne muscular dystrophy, FVC: Forced vital capacity, IV: intravenous, kg: kilogram, LVEF: Left ventricular ejection fraction, mg: milligram, n: number, N: total number, ULN: Upper Limit Normal, RNA: ribonucleic acid

Table D2. RCTs – Baseline Characteristics

Author / Trial Name & Year of Publication	Arm	N	Mean Age, years (SD)	Mean Height, cm (SD)	Mean Weight, kg (SD)	Mean BMI (SD)	Mean Age at Start of Treatment, years (SD)	Mean MRC score	Mean Motor Function Index	6MWT, meters	Rise time, seconds, mean (SD)	Total NSAA score, mean (SD)	FVC%p
Deflazacort (DFZ) vs. Prednisone (PRED)													
Griggs, 2016[106]	DFZ 0.9 mg/kg/day	51	8.8 (2.5)	131 (17)	31 (13)	17.1 (3.9)	NR						
	DFZ 1.2 mg/kg/day	49	8.8 (3.0)	130 (20)	29 (11)	16.7 (3.0)	NR						
	PRED 0.75 mg/kg/day	46	8.8 (2.9)	131 (18)	32 (15)	17.7 (4.2)	NR						
	Placebo	50	8.5 (3.1)	130 (18)	31 (15)	17.2 (3.6)	NR						
Karimzadeh, 2012[20]	DFZ 0.9 mg/kg/day	14	7.1 (1.98)	116.6 (11.65)	20.39 (4.63)	NR			4.93 (0.99)	NR			
	PRED 0.75 mg/kg/day	12	7.37 (1.27)	122.06 (9.05)	23.31 (3.95)	NR			5.0 (0.53)	NR			
Bonifati, 2000[21]	DFZ 0.9 mg/kg/day	10	8.6 (range 5.3-14.6)	NR				16.19*	NR				
	PRED 0.75 mg/kg/day	8	7.5 (range 5.1-10)	NR				15.48*	NR				
Eteplirsen													
Study 201/202[29,34]	Eteplirsen 30 mg/kg/week	4	9.3 (0.50)	130.5 (9.47)	34.8 (7.05)	NR	5.2 (1.9)	NR		355.3 (74.78)	8.2 (7.57)	24.9 (4.93)	NR
	Eteplirsen 50 mg/kg/week	4	8.5 (1.29)	121.3 (7.85)	29.0 (6.38)	NR		NR		396.0 (26.61)			NR
	Placebo (Study 201)	4	8.5 (1.73)	119.3 (3.40)	30.6 (6.04)	NR				394.5 (42.25)	---	---	NR
	Historical Control Group (Study 202)	13	9.45 (1.45)	NR		NR	6.4 (2.19)	NR		357.6 (66.75)	9.6 (10.25)	22.0 (6.27)	NR
Study 204[31,104]	Eteplirsen 30 mg/kg/day	24	13.04 (2.28)	127.30 (11,29)	48.71 (12.62)	NR							65.94 (16.6)
Study 301[31]	Eteplirsen 30 mg/kg/week	42	11.07 (1.44)	130.46 (7.24)	39.83 (11.16)	NR							78.48 (15.7)
	Untreated group	20	11.78 (2.24)	131.45 (7.60)	38.87 (14.78)	NR							79.60 (13.30)
Golodirsen													
Muntoni, 2018[135]	Golodirsen 30 mg/kg/week	8	NR										
	Placebo (Part 1)	4	NR										
	Untreated group (Part 2)	24	NR										

*digitized from publication and should be interpreted with caution.

6MWT: 6-minute walking test, BMI: body mass index, FVC%p: forced vital capacity percent predicted, MRC: Medical Research Council, NR: not reported, NSAA: North Star Ambulatory Assessment, SD: standard deviation

Table D3. RCTs – Efficacy Outcomes for Corticosteroids

Author & Year of Publication	Arm	N	Muscle Strength		Motor Function (Compound Measure)		Time from Supine to Standing, Seconds		Time to Climb 4 Stairs, Seconds		Time to Run/Walk 30 Feet, Seconds		Pulmonary Function (FVC)	
			MRC LSM Change (95%CI)	Δ Treatment (95% CI), p-Value	MRC LSM Change (95%CI)	Δ Treatment (95% CI), p-Value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value
Deflazacort (DFZ) vs. Prednisone (PRED)														
Griggs, 2016[106]	DFZ 0.9 mg/kg/ day	48	At 12 w 0.15 (0.01, 0.28)	At 12 w 0.25 (0.04, 0.46), p=0.017	NR		At 12 w Improvement	At 12 w p<0.0018	At 12 w Improvement	At 12 w p<0.0001	At 12 w Improvement	At 12 w p<0.0001	NR	
		41	12 – 52 w 0.17 (0.03, 0.31)	12 – 52 w 0.29 (0.08, 0.49), p=0.044	NR		12 – 52 w Numerically better	12 – 52 w n.s.	12 – 52 w Numerically better	12 – 52 w n.s.	12 – 52 w Numerically better	12 – 52 w n.s.	NR	
		41	At 52 w 0.39 (0.25, 0.54)	At 52 w n.s.	NR		NR		At 52 w Improvement	At 52 w p=0.046	NR		No diff.	n.s.
	DFZ 1.2 mg/kg/ day	46	At 12 w 0.26 (0.12, 0.40)	At 12 w 0.36 (0.14, 0.57), p=0.0003	NR		At 12 w Improvement	At 12 w p=0.0002	At 12 w Improvement	At 12 w p<0.0001	At 12 w Improvement	At 12 w p<0.0001	NR	
		34	12 – 52 w 0.04 (-0.11, 0.19)	12 – 52 w 0.16 (-0.06, 0.37), p=0.18	NR		12 – 52 w Numerically better	12 – 52 w n.s.	12 – 52 w Numerically better	12 – 52 w n.s.	12 – 52 w Numerically better	12 – 52 w n.s.	NR	
		34	At 52 w 0.38 (0.23, 0.54)	At 52 w n.s.	NR		NR		At 52 w Improvement	At 52 w p=0.0012	NR		Greater benefit	sign.
	PRED 0.75 mg/kg/ day	45	At 12 w 0.27 (0.13, 0.41)	At 12 w 0.37 (0.15, 0.59), p=0.0002	NR		At 12 w Improvement	At 12 w p=0.0016	At 12 w Improvement	At 12 w p<0.0001	At 12 w Improvement	At 12w p<0.0001	NR	
		37	12 – 52 w -0.12 (-0.26, 0.03)	12 – 52 w ---	NR		12 – 52 w ---	12 – 52 w ---	12 – 52 w ---	12 – 52 w ---	12 – 52 w ---	12 – 52 w ---	NR	
		37	At 52 w 0.23 (0.07, 0.38)	At 52 w ---	NR		At 52 w ---	At 52 w ---	At 52 w ---	At 52 w ---	At 52 w ---	At 52 w ---	---	---
	Placebo	50	At 12 w -0.10 (-0.23,	At 12 w ---	NR		At 12 w ---	---	At 12 w ---	---	At 12 w ---	---	NR	

Author & Year of Publication	Arm	N	Muscle Strength		Motor Function (Compound Measure)		Time from Supine to Standing, Seconds		Time to Climb 4 Stairs, Seconds		Time to Run/Walk 30 Feet, Seconds		Pulmonary Function (FVC)	
			MRC LSM Change (95%CI)	Δ Treatment (95% CI), p-Value	MRC LSM Change (95%CI)	Δ Treatment (95% CI), p-Value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value	MRC LSM Change (95%CI)	p-value
			0.03)											
Karimzadeh, 2012[20]	DFZ 0.9 mg/kg/ day	14	NR		At 12 m -0.57 (1.08)† At 18 m -0.29 (0.89)†	At 12 m p=0.001 At 18 m p=0.128	NR							
	PRED 0.75 mg/kg/ day	12	NR		At 12 m 0.25 (1.08)† At 18 m (n=8) 0.75 (1.48)†	---	NR							
Bonifati, 2000[21]	DFZ 0.9 mg/kg/ day	10	0.91*	n.s.	-1.2*	n.s.	NR							
	PRED 0.75 mg/kg/ day	8	0.87*	---	-2.1*	---	NR							
	Natural History	7	-4.03*	NR	3.7*	NR	NR							

*Digitized and should be interpreted with caution. † SD calculated with correlation coefficient assumed to be 0.5.

CI: confidence interval, diff.: difference, LSM: least square mean, m: months, MRC: Medical Research Council, N: total number, NR: not reported, ns: not significant, sign: significant, w: weeks

Table D4. RCTs – Efficacy Outcomes for Gene Therapies

Trial Name & Year of Publication	Arm	N	6MWT, m		NSAA	Dystrophin Levels		FVC%p	
			Mean Change (SE)	Δ Treatment (95% CI), p-Value	Mean Change	Mean % Change (SE)	Δ Treatment (95% CI), p-Value	Mean Annual Change (SE)	Δ Treatment (95% CI), p-Value
Eteplirsen									
Study 201[29,31,136]	Eteplirsen 30 mg/kg/week	4	-128.2 (31.6)	NR (NR), p≤0.001	NR	24 weeks 22.9 (2.90)	24 weeks NR (NR), p≤0.002	NR	
	Eteplirsen 50 mg/kg/week	4	-0.3 (31.2)		NR	12 weeks 0.8 (3.55)	12 weeks n.s.	NR	
	Placebo	4	-25.8 (30.6)	---	NR	12 weeks -4.0 (2.92)	---	NR	
Study 202[30,31]	Eteplirsen 30 mg/kg/week	6	-166.9 (NR)	163.4 (NR), p=0.0005	-10.9 (3 years follow-up)	NR	0.85%	-2.19 (0.71)	NR (-3.60, -0.79), p<0.001
	Eteplirsen 50 mg/kg/week	6							
	Historical Control	13	-330.3 (NR)	---	-11.9 (3 years follow-up)		---	3.80 (0.819)	---
Study 204[30,31]	Eteplirsen 30 mg/kg/week	24	NR					-3.66 (0.68)	N/A
Study 301[31]	Eteplirsen 30 mg/kg/week	42	NR					-3.79 (0.82)	NR (-5.41, -2.16), p=0.017
	Untreated control group	20	NR					2.21 (0.92)	---
Golodirsen									
Muntoni 2018[135]	Golodirsen 30 mg/kg/week	8	NR						
	Placebo	4	NR						
	Untreated group not amenable to exon 53 skipping	24	NR						

6MWT: 6-minute walk test, CI: confidence interval, N: total number, N/A: not available, NR: not reported, NSAA: North Star Ambulatory Assessment, SE: standard error

Table D5. RCTs – Harms I for Corticosteroids

Author & Year of Publication	Arm	N	Any AEs, n (%)	AEs Leading to D/C, n (%)	SAEs, n (%)	Death, n (%)	Cushingoid, n (%)	Erythema, n (%)	Hirsutism, n (%)	Central Obesity, n (%)	Weight Gain		Height, Mean Change (95% CI), cm (SD)	BMI	Abnormal Behavior, n (%)	Cataracts, n (%)
											n (%)	Mean Change, kg (95% CI)				
Deflazacort vs. Prednisone																
Griggs, 2016[106]	DFZ 0.9 mg/kg/day	68	58 (85.3)	3 (5.9)	NR	1 (1.96)	41 (60.3)	19 (27.9)	24 (35.3)	17 (25.0)	19 (27.9)	3.64* (2.90, 4.38)	NR	NR	6 (8.8)	3 (4.4)
	DFZ 1.2 mg/kg/day	65	56 (86.2)	3 (6.1)	NR	0 (0)	45 (69.2)	32 (49.2)	24 (36.9)	16 (24.6)	21 (32.3)	4.16† (3.37, 4.94)	NR	NR	4 (6.2)	1 (1.5)
	PRED 0.75 mg/kg/day	63	58 (92.1)	4 (8.7)	NR	1 (2.2)	49 (77.8)	33 (52.4)	28 (44.4)	27 (42.9)	22 (34.9)	5.57 (4.76, 6.37)	NR	NR	9 (14.3)	1 (1.6)
	Placebo	50	38 (76.0)	---	NR	---	6 (12.0)	3 (6.0)	1 (2.0)	2 (4.0)	3 (6.0)	1.23 (0.00, 2.46)	NR	NR	3 (6.0)	---
Karimzadeh, 2012[20]	DFZ 0.9 mg/kg/day	14	NR	0 (0)	NR							4.32‡	6.79 (NR), 123.39 (12.20)	NR		0 (0)
	PRED 0.75 mg/kg/day	8	NR	4/12 (33.3)	NR							7.5	6.25 (NR), 128.31 (8.8)	NR		0 (0)
Bonifati, 2000[21]	DFZ 0.9 mg/kg/day	10	NR	0 (0)	NR		5 (55)	NR	5 (55)	NR	>20%: 1 (11)	2.17§ / % change: 9%	NR		6 (66)	2 (22)
	PRED 0.75 mg/kg/day	8	NR	1 (11) due to LoA	NR		4 (50)	NR	3 (37)	NR	>20%: 4 (50)	5.08 / % change: 21.3%*	NR		5 (62)	1 (11)

* p=0.003 (compared to PRED), † p=0.013 (compared to PRED), ‡ p=0.046 (compared to PRED), § p<0.05 (compared to PRED)

AEs: adverse events, BMI: body mass index, CI: confidence interval, cm: centimeter, D/C: discontinuation, kg: kilogram, n: number, N: total number, NR: not reported, SAEs: serious adverse events, SD: standard deviation

Table D6. RCTs – Harms II for Corticosteroids

Author/Trial Name & Year of Publication	Arm	N	Headache, n (%)	Nasopha-ryngitis, n (%)	Incr. Appetite, n (%)	Abdom. Pain, n (%)	Upper Resp. Tract Infection, n (%)	Cough, n (%)	Influenza, n (%)	Consti-pation, n (%)	Polla-kiuria, n (%)	Pyrexia, n (%)	Growth Delay, n (%)	Fractures, n (%)	Sleep Disturb ., n (%)	Cardio-myopathy, n (%)
Griggs, 2016[106]	DFZ 0.9 mg/kg/day	68	15 (22.1)	16 (23.5)	8 (11.8)	6 (8.8)	10 (14.7)	7 (10.3)	4 (5.9)	7 (10.3)	10 (14.7)	6 (8.8)	NR			
	DFZ 1.2 mg/kg/day	65	22 (33.8)	15 (23.1)	8 (12.3)	9 (13.8)	6 (9.2)	8 (12.3)	10 (15.4)	10 (15.4)	8 (12.3)	4 (6.2)	NR			
	PRED 0.75 mg/kg/day	63	22 (34.9)	10 (15.9)	12 (19.0)	10 (15.9)	7 (11.1)	8 (12.7)	10 (15.9)	4 (6.3)	3 (4.8)	6 (9.5)	NR			
	Placebo	50	11 (22.0)	3 (6.0)	1 (2.0)	4 (8.0)	5 (10.0)	3 (6.0)	2 (4.0)	3 (6.0)	1 (2.0)	4 (8.0)	NR			
Karimzadeh, 2012[20]	DFZ 0.9 mg/kg/day	14	NR													0 (0)
	PRED 0.75 mg/kg/day	8	NR													0 (0)
Bonifati, 2000[21]	DFZ 0.9 mg/kg/day	10	NR		3 (33)	NR								1 (10)	0 (0)	NR
	PRED 0.75 mg/kg/day	8	NR		6 (75)	NR								0 (0)	0 (0)	NR

Abdom.: abdominal, disturb.: disturbance, incr.: increased, n: number, N: total number, NR: not reported, resp: respiratory

Table D7. Harms I for Gene Therapies

Trial Name & Year of Publication	Arm	N	SAEs, n (%)	Death, n (%)	AEs leading to d/c, n (%)	Loss of Ambulation, n (%)	Headache, n (%)	Nasopharyngitis, n (%)	Vomiting, n (%)	Abdominal pain, n (%)	Oropharyngeal pain, n (%)
Eteplirsen											
Study 201[136]	Eteplirsen 30 mg/kg/ week	4	0 (0)	0 (0)	0 (0)	NR	1 (25)	0 (0)	1 (25)	0 (0)	3 (75)
	Eteplirsen 50 mg/kg/ week	4	0 (0)	0 (0)	0 (0)	NR	0 (0)	0 (0)	2 (50)	0 (0)	0 (0)
	Placebo	4	0 (0)	0 (0)	0(0)	NR	2 (50)	1 (25)	0 (0)	2 (50)	3 (75)
Study 202[30]	Eteplirsen 30 mg/kg/ week	6	0 (0)	0 (0)	0 (0)	2 (16.7)	NR				
	Eteplirsen 50 mg/kg/ week	6	0 (0)	0 (0)	0 (0)		NR				
	Historical Control Group	13	0 (0)	0 (0)	0 (0)	10 (76.9)	NR				
Study 204[137]	Eteplirsen 30 mg/kg/ week	24	4 (16.7)	0 (0)	2 (8.33)	NR	8 (33.3)	14 (58.3)	7 (29.2)	6 (25)	5 (20.4)

AEs: adverse events, d/c: discontinuation, mg: milligram, n: number, N: total number, NR: not reported, SAEs: serious adverse events

Table D8. Harms II for Gene Therapies

Trial Name & Year of Publication	Arm	N	Upper Respiratory Tract Infection, n (%)	Cough, n (%)	Pyrexia, n (%)	Injection Site Pain, n (%)	Procedural Pain, n (%)	Hypokalemia, n (%)	Hematoma, n (%)	Osteoporosis, n (%)
Eteplirsen										
Study 201[136]	Eteplirsen 30 mg/kg/ week	4	1 (25)	1 (25)	1 (25)	0 (0)	1 (25)	2 (50)	1 (25)	NR
	Eteplirsen 50 mg/kg/ week	4	0 (0)	1 (25)	0 (0)	1 (25)	3 (75)	2 (50)	1 (25)	NR
	Placebo	4	0 (0)	2 (50)	2 (50)	0 (0)	3 (75)	2 (50)	1 (25)	NR
Study 202[30]	Eteplirsen 30 mg/kg/ week	6	NR							
	Eteplirsen 50 mg/kg/ week	6	NR							
Study 204[137]	Eteplirsen 30 mg/kg/ week	24	6 (25)	7 (29.2)	3 (12.5)	2 (8.3)	4 (16.7)	NR		2 (8.33)

kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported

Table D9. Evidence Tables for Observational Studies

Author & Year of Publication	Study Design, Location, Duration of Follow-up, total N	Interventions (n) & Dosing Schedule	Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms, n (%)
Deflazacort (DFZ) vs. Prednisone/Prednisolone (PRED)						
Joseph, 2019[22]	Multicenter, retrospective review of UK NorthStar database UK Follow-up: variable (up to 5 years) N: 193	– Daily DFZ (n=41) – Daily PRED (n=152)	Inclusion Criteria DMD diagnosis Exclusion Criteria NR	DFZ – Median age, years (range): 7.4 (5.8- 10.5) – Non-ambulant at BL n (%): 1 (2) PRED – Median age, years (range): 7.0 (5.3 - 8.3) – Non-ambulant at BL n/N (%): 21/131 (16) GC naïve – Median age, years (range): 5.3 (4.0 - 6.5) – Non-ambulant at BL, no (%): 0 (0)	NR (Fractures as key outcome: see harms)	DFZ – Factures: Incidence per 10,000 person-years (95% CI): 1367 (796-2188) PRED – Fractures: Incidence per 10,000 person-years (95% CI): 748 (550-995)
Shieh, 2018[23]	Post hoc analysis from ACT DMD trial (NCT01826487) US Follow-up: 48 weeks N: 114	DFZ – Daily (84.3%) – Every other day (13.7%), – Twice a day (2.0%) PRED – Daily (64.4%) – Every other day (16.9%) – 10 days on/ 10 days off (10.2%) – High-dose	Inclusion Criteria Male; 7-16 years; phenotypic evidence of dystrophinopathy (onset of clinical symptoms/signs by 6 years of age); ≥6 months of CS treatment; no dosing change within 3 months; ability to walk ≥150 m unassisted during 6MWT screening Exclusion Criteria Treatment with systemic aminoglycoside antibiotics within prior 3 months; changes in prophylaxis/ treatment for congestive heart failure within prior 3 months; treatment with	DFZ (daily) – Mean age, years (SD): 9.2 (1.7) – Mean height, cm (SD): 127.0 (10.6) – Mean weight, kg (SD): 30.9 (11.9) – Mean BMI (SD): 18.6 (4.70) – Mean 6MWT distance, meters (SD): 361.3 (87.7) – Mean duration for 4-stairs climb, seconds (SD): 6.4 (6.9) – Mean duration for rise from supine, seconds (SD): 8.7 (7.7) – Mean duration for 10m walk/run, seconds (SD): 6.6 (3.2) PRED (daily) – Mean age, years (SD): 8.8 (1.6)	*Mean Change, SE* Time from supine to standing, seconds – DFZ: 4.50 (1.24) – PRED: 7.10 (1.13) – Between-group diff. (95%CI), p-value: -2.60 (-5.20, 0.01), n.s. (p-value NR) Time to Climb 4 stairs, seconds – DFZ: 3.79 (1.13) – PRED: 6.67 (1.0) – Between-group diff. (95%CI), p-value: -2.88 (-5.27, -0.48), significant (p-value NR) Time to run/walk 10m, seconds – DFZ: 3.16 (0.93) – PRED: 3.25 (0.85)	DFZ AEs leading to discontinuation: 1 (2); SAEs: 3 (6); Weight gain, mean change (SD): 3.9 kg (2.6); Height, mean change (SD): 3.2 (2.0); BMI, mean change (SD): 1.3 (1.3); Cushingoid: 0 (0); Hirsutism: 0 (0); Headache: 10 (19); Cataracts: 0 (0); Nasopharyngitis: 6 (11); Abdominal pain: 0 (0); Upper respiratory tract infection: 0 (0); Cough: 5 (9); Constipation: 4 (8); Pyrexia: 4 (8); Fractures: 2 (3.8) PRED AEs leading to discontinuation: 0 (0); SAEs: 1 (1.6); Weight gain, mean

		weekend (8.5%)	coumarin-based anticoagulants, phenytoin, tolbutamide, or paclitaxel; exposure to another investigational drug within 3 months prior to study; major surgical procedure within 6 weeks prior to study; immunosuppressive therapy (other than corticosteroids); requirement for daytime ventilator assistance; expected surgery (e.g., scoliosis surgery) during 12 month study follow-up	– Mean height, cm (SD): 125.7 (10.4) – Mean weight, kg (SD): 30.5 (9.2) – Mean BMI (SD): 19.0 (3.5) – Mean 6MWT distance, meters (SD): 365.5 (76.0) – Mean duration for 4-stairs climb, seconds (SD): 64 (4.3) – Mean duration for rise from supine, seconds (SD): 10.4 (7.9) – Mean duration for 10m walk/run test: 7.0 (2.6)	– Between-group diff. (95%CI), p-value: -0.09 (-2.07, 1.89), n.s. (p-value NR) 6MWT, meters – DFZ: -39.01 (15.05) – PRED: -70.59 (13.40) – Between-group diff. (95%CI), p-value: 31.6 (0.22, 62.94), significant (p-value NR) Time to Loss of Ambulation, years – DFZ: 8.58 – PRED: 4.74 – Between-group diff. (95%CI), p-value: 3.84 (-2.43, 10.11), n.s. (p-value NR)	change (SD): 4.6 kg (3.2); Height, mean change (SD): 3.9 (1.9); BMI, mean change (SD): 1.6 (1.5); Cushingoid: 0 (0); Hirsutism: 0 (0); Headache: 11 (18); Cataracts: 0 (0); Nasopharyngitis: 17 (27); Abdominal pain: 18 (29); Upper respiratory tract infection: 6 (10); Cough: 8 (13); Constipation: 6 (10); Pyrexia: 8 (13); Fractures: 0 (0)
McDonald, 2018[24]	Prospective cohort study US Follow-up: 10 years N: 440	DFZ – Variable dosing schedules – Daily (n=107) PRED – Variable dosing schedules – Daily (n=40)	Inclusion Criteria Male; 2-28 years; confirmed DMD diagnosis Exclusion Criteria Steroid naïve and ambulated past 13 years of age; ambulated past 16 years of age despite steroid treatment	– Mean age, years (SD): 10.7 (5.7) – Ambulatory, n (%): 292 (66) – Non-Ambulatory, n (%): 148 (34)	*Median, SE* Age at loss of ability to rise from supine to standing – DFZ: 13.10 (1.39) – PRED: 11.04 (0.31) – Log-rank p-value: 0.0114 Age at loss of ability to climb 4-stairs – DFZ: 14.13(0.57) – PRED: 12.02 (0.59) – Log rank p-value: 0.09 Age at loss of ambulation DFZ: 14.00 (0.20) PRED: 11.30 (0.42) Log-rank p-value: 0.0102 Age at loss of hand to mouth function; Brooke ≥5) – DFZ: 20.48 (0.90) – PRED: 17.77 (0.94) – Log-rank p-value: 0.0110	– Person-years exposure to daily DFZ: 191 – Person-years exposure to PRED: 877 – 45 patients died during 10-year follow-up period Daily DFZ, n (%) Weight gain: 48 (5); Cushingoid: 57 (6); Behavior changes: 26 (3); Growth delay: 45 (5); Fractures: 12 (1); Cataracts: 26 (3); Hirsutism: 6 (<1); Low bone density: 0 (0); Headache: 1 (<1); Sleep disturbances: 0 (0); stomach pain: 0 (0) Daily PRED, n (%) Weight gain: 26 (14); Cushingoid: 17 (9); Behavior changes: 11 (6); Growth delay: 8 (4); Fractures: 6 (3); Cataracts: 1 (<1); Hirsutism: 1 (<1); Low bone density: 1 (<1); Headache: 0 (0); Sleep disturbance: 0 (0); Stomach pain: 0 (0)
Lamb, 2016[25]	MD STARnet database	– At least daily DFZ	Inclusion Criteria DMD diagnosis; 2-12 years	DFZ – Mean age at start of treatment, years (SD): 6.5 (1.6)	---	– DFZ leads to less weight gain compared to PRED (p=0.005)

	US Follow-up: 6 years N: 147	– At least daily PRED	Exclusion Criteria Steroid treatment <6 months; medical comorbidities; no growth records	PRED – Mean age at start of treatment, years (SD): 6.6 (1.8)		– DFZ associated with shorter stature compared to PRED (p<0.0001) – BMI is equivalent between DFZ and PRED (p=0.53)
Bello, 2015[27]	CINRG Duchenne Natural History Study International Follow-up: variable (on average 4 years) N: 174	– Daily DFZ (n=80) – Daily PRED (n=94)	Inclusion Criteria Male; 2-28 years; confirmed DMD diagnosis Exclusion Criteria Steroid naïve and ambulated past 13 years of age; ambulated past 16 years of age despite steroid treatment	DFZ – Age at start of treatment, mean (SD): 7.2 (2.0) years PRED – Age at start of treatment, mean (SD): 6.6 (1.9) years	Age at Loss of Ambulation, median (years) – DFZ: 13.9 – PRED: 11.2 – Log-rank p-value: p<0.001	DFZ Weight gain: (63); Cushingoid: (72); Behavior change: (33); Growth delay: (60); Cataracts: (29) Low BMD or fracture: (25); Hirsutism: (5); Stomach pain: (3); Headache: (3); Sleep disturbance: (0) PRED Weight gain: (67); Cushingoid: (50); Behavior change: (30); Growth delay: (27); Cataracts: (5); Low BMD or fracture: (22); Hirsutism: (10); Stomach pain: (2); Headache: (1); Sleep disturbance: (1)
Kim, 2015[26]	Longitudinal observational surveillance project; MDSTAR*net* US Follow-up: 29 years N: 477	DFZ – Short-term (3 months – 3 years): n=25 – Long-term (>3 years): n=24 PRED – Short-term (3 months – 3 years): n=78 – Long-term (>3 years): n=63 Untreated:	Inclusion Criteria Initiated treatment between ages 5 and 10 years Exclusion Criteria No data on mobility; comorbid condition; inconsistent data; likely BMD; corticosteroid treatment ≤3 months	DFZ – Mean age at start of treatment (SE): 6.8 (0.2) years – Treatment duration, mean (SE): 3.6 (0.3) years PRED – Mean age at start of treatment (SE): 7.1 (0.1) years – Treatment duration, mean (SE): 3.1 (0.2) years	Age at Loss of Ambulation, mean years (SE) – Short-term DFZ (n=12): 9.6 (0.3), p<0.05 – Short-term PRED (n=55): 9.4 (0.2), p<0.05 – Long-term DFZ (n=11): 12.6 (0.6), p<0.05 – Long-term PRED (51): 12.3 (0.2), p<0.05 – Untreated (n=162): 10.3 (0.1), reference group	NR

		n=257				
Balaban, 2005[28]	Retrospective, observational study US Follow-up: 7 years N: 30	– DFZ 0.9 mg/kg/day (n=12) – PRED 0.75 mg/kg/day (n=18)	Inclusion Criteria Male; confirmed DMD diagnosis; onset of weakness < 5 years of age; initial proximal muscle weakness with pseudohypertrophy; increased serum creatine kinase Exclusion Criteria Change between different types of steroids; started steroid after loss of walking; additional disease comorbidities	DFZ – Mean age, years (SD): 14.08 (1.60) – Mean weight, kg (SD): 20.25 (1.90) – Mean age at start of treatment, years (SD): 7.45 (0.97) PRED – Mean age, years (SD): 14.60 (0.98) – Mean weight, kg (SD): 21.0 (2.0) – Mean age at start of treatment, years (SD): 6.90 (1.0)	*Mean Survival Time, years* DFZ Walking: 10.94-12.89, p=0.421 Getting up: 10.85-12.65, p=0.393 Climbing: 10.65-12.58, p=0.544 Standing up: 10.97-12.69, p=0.476 Lifting weight: 11.26 – 14.07, p=0.897 Lifting hand: 12.03 – 14.64, p=0.967 PRED (reference group) Walking: 10.61-12.38 Getting up: 10.22-11.95 Climbing: 10.36-12.08 Standing up: 10.38-12.17 Lifting weight: 11.15-13.00 Lifting hand: 11.90-14.00	DFZ, n (%) AEs leading to discontinuation: 0 (0); Abnormal behavior: 1 (8.3); Cataracts 2 (16.7); Fractures: 1 (8.3); Tapered treatment: 3 (25) PRED, n (%) AEs leading to discontinuation: 5 (27.8); Abnormal behavior: 3 (16.7); Cataracts 0 (0); Fractures: 1 (5.6);

6MWT: 6-minute walk test, AEs: adverse events, BMD: Becker muscular dystrophy, BMI: body mass index, CI: confidence interval, cm: centimeter, CS: corticosteroid, diff.: difference, DMD: Duchenne muscular dystrophy, kg: kilogram, n: number, N: total number, NR: not reported, n.s.: not significant, SD: standard deviation, SE: standard error, SAEs: serious adverse events

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[138]

Table E2. The Akaike Information Criterion (AIC) of All Distributions for Late Ambulatory, Early Non-Ambulatory, and Overall Survival Curves

Distribution	Late Ambulatory Survival Curve AIC	Early Non-Ambulatory Survival Curve AIC	Overall Survival Curve AIC
Exponential	3,159.77	2,382.84	3,167.87
Weibull	2,696.91	2,083.96	2,730.47
Logistic	2,751.60	2,113.44	2,776.88
Log-Logistic	2,662.98	2,077.31	2,712.30
Log-Normal	2,660.55	2,068.12	2,695.96

Table E3: The Parameterization of the Late Ambulatory, Early Non-Ambulatory, and Overall Survival Curves

Parameters	Late Ambulatory Survival Curve	Early Non-Ambulatory Survival Curve	Overall Survival Curve
Intercept	2.126	2.509	2.956
Log Scale	-0.744	-0.789	-0.836

Table E4: The Cholesky Decomposition of the Late Ambulatory Survival Curve

Ambulatory Survival Cholesky	Intercept	Log Scale
Intercept	0.020	0.000
Log Scale	0.018	0.033

Table E5: The Cholesky Decomposition of the Early Non-Ambulatory Survival Curve

Ambulatory Survival Cholesky	Intercept	Log Scale
Intercept	0.031	0.000
Log Scale	0.042	0.034

Table E6: The Cholesky Decomposition of the Overall Survival Curve

Overall Survival Cholesky	Intercept	Log Scale
Intercept	0.022	0.000
Log Scale	0.026	0.033

Table E7. Tornado Diagram Inputs and Results for Deflazacort versus Prednisone from the Health Sector Perspective

Input Name	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Treatment Shift (Deflazacort)	$470,790	$276,046	1	5
Early Ambulation Patient Utility	$473,093	$292,144	0.58	0.88
Deflazacort Drug Cost ($/mg)	$292,018	$430,431	$4.95	$7.43
Deflazacort Discontinuation	$350,313	$372,132	0.31	0.47
Late Ambulation Patient Utility	$353,408	$369,395	0.51	0.77
Early Ambulatory Direct Medical (Non-Medication) Costs	$355,680	$370,410	$15,206	$24,300
Late Non-Ambulation Patient Utility	$358,183	$364,318	0.14	0.22
Early Non-Ambulation Patient Utility	$358,803	$363,679	0.17	0.25
Late Non-Ambulatory Direct Medical (Non-Medication) Costs	$362,810	$358,599	$29,849	$47,702
Early Non-Ambulatory Direct Medical (Non-Medication) Costs	$362,031	$359,889	$22,286	$35,616

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.
ICER: incremental cost effectiveness ratio

Table E8. Tornado Diagram Inputs and Results for Deflazacort versus Prednisone from the Modified Societal Perspective

Input Name	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Early Ambulation Patient Utility	$510,479	$315,231	0.58	0.88
Treatment Shift (Deflazacort)	$499,258	$304,653	1	5
Deflazacort Drug Cost ($/mg)	$320,565	$458,977	$4.95	$7.43
Deflazacort Discontinuation	$378,865	$400,671	0.31	0.47
Late Ambulation Patient Utility	$381,336	$398,587	0.51	0.77
Early Ambulatory Direct Medical (Non-Medication) Costs	$384,226	$398,956	$15,206	$24,300
Early Ambulatory Indirect Cost of Illness Costs	$385,806	$393,877	$14,790	$19,773
Late Non-Ambulation Patient Utility	$386,489	$393,108	0.14	0.22
Early Non-Ambulation Patient Utility	$387,158	$392,419	0.17	0.25
Early Ambulatory Non-Medical Community Services Costs	$387,724	$392,595	$4,823	$7,831

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.
ICER: incremental cost effectiveness ratio

Table E9: Table of Parameters in the Model and Respective Distribution, Mean, and Standard Errors

Parameters	Distribution	Mean	Standard Error
Prednisone Cataracts Rate	Beta	0.00	0.00
Prednisone Weight Gain Rate	Beta	0.01	0.00
Prednisone Cushingoid Rate	Beta	0.01	0.00
Prednisone Behavior Change Rate	Beta	0.01	0.00
Prednisone Fractures Rate	Beta	0.00	0.00
Deflazacort Cataracts Rate*	Beta	0.00	0.00
Deflazacort Cataract Surgery Ratio	Log Normal	0.07	0.10
Deflazacort Weight Gain Rate	Beta	0.01	0.00
Deflazacort Cushingoid Rate	Beta	0.01	0.00
Deflazacort Behavior Change Rate	Beta	0.00	0.00
Deflazacort Fractures Rate	Beta	0.00	0.00
Prednisone Discontinuation Rate	Beta	0.39	0.04
Deflazacort Discontinuation Rate	Beta	0.39	0.04
Prednisone Drug Cost ($/mg)	Gamma	$0.05	$0.01
Deflazacort Drug Cost ($/mg)	Gamma	$6.19	$1.24
Early Ambulatory Direct Medical (Non-Medication) Costs	Gamma	$18,629	$3,423
Early Ambulatory Medications Costs	Gamma	$1,656	$280
Early Ambulatory Aids and Devices Costs	Gamma	$2,296	$498
Early Ambulatory Non-Medical Community Services Costs	Gamma	$6,087	$1,264
Early Ambulatory Informal Care Costs	Gamma	$10,694	$1,048
Early Ambulatory Indirect Cost of Illness Costs	Gamma	$17,237	$2,448
Early Ambulatory Out of Pocket for Investments Costs	Gamma	$4,047	$878
Late Ambulatory Direct Medical (Non-Medication) Costs	Gamma	$18,462	$3,393
Late Ambulatory Medications Costs	Gamma	$1,641	$277

Parameters	Distribution	Mean	Standard Error
Late Ambulatory Aids and Devices Costs	Gamma	$2,275	$493
Late Ambulatory Non-Medical Community Services Costs	Gamma	$6,032	$1,252
Late Ambulatory Informal Care Costs	Gamma	$10,598	$1,038
Late Ambulatory Indirect Cost of Illness Costs	Gamma	$17,083	$2,426
Late Ambulatory Out of Pocket for Investments Costs	Gamma	$4,011	$870
Early Non-Ambulatory Direct Medical (Non-Medication) Costs	Gamma	$27,304	$5,018
Early Non-Ambulatory Medications Costs	Gamma	$2,427	$410
Early Non-Ambulatory Aids and Devices Costs	Gamma	$3,365	$730
Early Non-Ambulatory Non-Medical Community Services Costs	Gamma	$8,922	$1,852
Early Non-Ambulatory Informal Care Costs	Gamma	$15,674	$1,536
Early Non-Ambulatory Indirect Cost of Illness Costs	Gamma	$25,264	$3,587
Early Non-Ambulatory Out of Pocket for Investments Costs	Gamma	$5,932	$1,287
Late Non-Ambulatory Direct Medical (Non-Medication) Costs	Gamma	$36,570	$6,720
Late Non-Ambulatory Medications Costs	Gamma	$3,250	$550
Late Non-Ambulatory Aids and Devices Costs	Gamma	$4,506	$977
Late Non-Ambulatory Non-Medical Community Services Costs	Gamma	$11,949	$2,481
Late Non-Ambulatory Informal Care Costs	Gamma	$20,993	$2,057
Late Non-Ambulatory Indirect Cost of Illness Costs	Gamma	$33,837	$4,805
Late Non-Ambulatory Out of Pocket for Investments Costs	Gamma	$7,945	$1,723
Cataracts AE Costs	Gamma	$75	$38
Cataract Surgery AE Costs	Gamma	$3,434	$1,717

Parameters	Distribution	Mean	Standard Error
Weight Gain AE Costs	Gamma	$75	$38
Cushingoid AE Costs	Gamma	$75	$38
Behavior Change AE Costs	Gamma	$75	$38
Fractures AE Costs	Gamma	$7,661	$3,831
Early Ambulation Patient Utility	Beta	0.730	0.074
Late Ambulation Patient Utility	Beta	0.640	0.065
Early Non-Ambulation Patient Utility	Beta	0.210	0.021
Late Non-Ambulation Patient Utility	Beta	0.180	0.018
Early Ambulation Caregiver Utility	Beta	0.858	0.080
Late Ambulation Caregiver Utility	Beta	0.839	0.084
Early Non-Ambulation Caregiver Utility	Beta	0.784	0.080
Late Non-Ambulation Caregiver Utility	Beta	0.810	0.083
Cataracts Disutility	Gamma	0.05	0.03
Cataracts Surgery Disutility	Gamma	0.05	0.03
Weight Gain Disutility	Gamma	0.05	0.03
Cushingoid Disutility	Gamma	0.05	0.03
Behavior Change Disutility	Gamma	0.05	0.03
Fractures Disutility	Gamma	0.05	0.03

*Because the prednisone rate of cataract surgery was 0 out of 596, we left the rate out of the PSA

AE: adverse event, mg: milligram, mL: milliliter

Table E10. Results of Probabilistic Sensitivity Analysis for Deflazacort versus Prednisone

	Deflazacort		Prednisone		Incremental	
	Mean	Credible Range (95% CI)	Mean	Credible Range (95% CI)	Mean	Credible Range (95% CI)
Total						
Total Costs	$1,030,000	$736,000 to $1,350,000	$473,000	$330,000 to $619,000	$556,000	$369,000 to $779,000
Total QALYs	8.47	6.58 to 10.27	6.93	5.54 to 8.26	1.54	1.02 to 2.04
ICER	--	--	--	--	$370,000	$88,000 to $531,000

CI: confidence interval, ICER: incremental cost effectiveness ratio, QALY: quality-adjusted life years

Figure E1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds

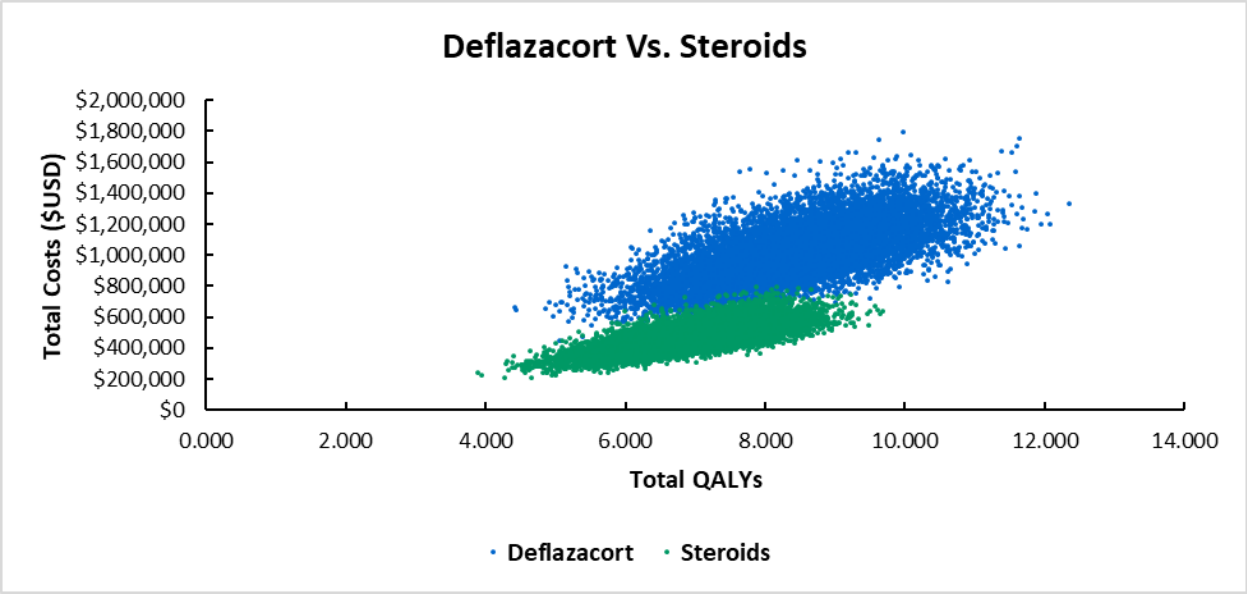
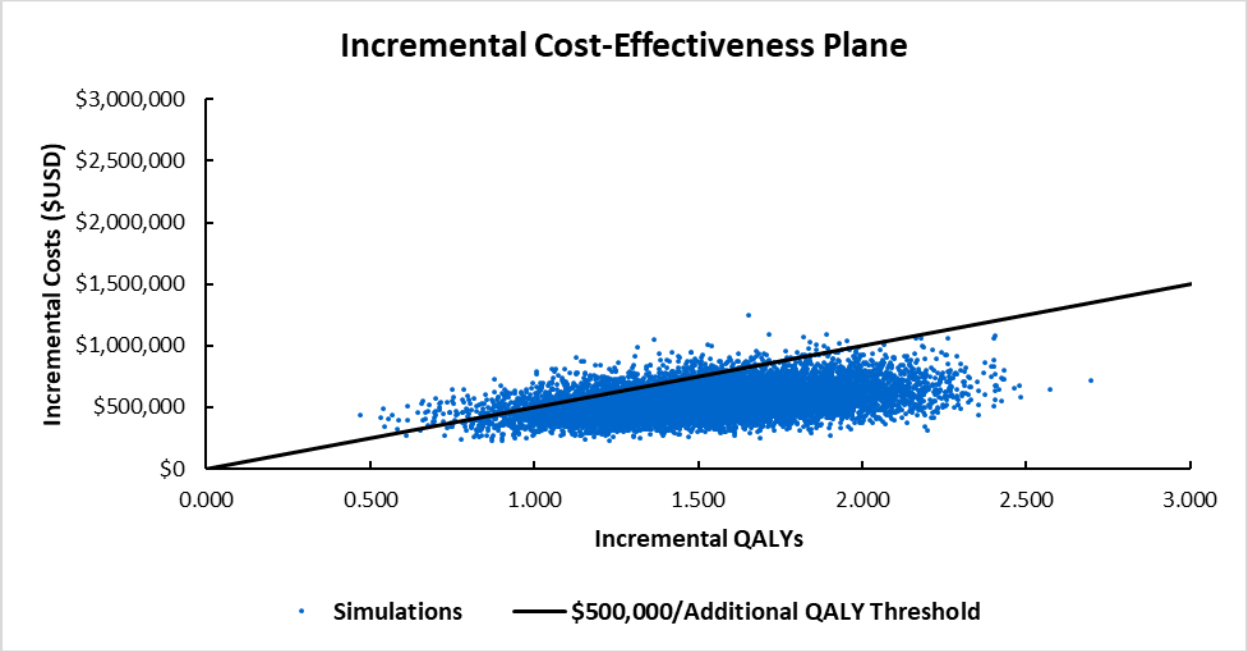
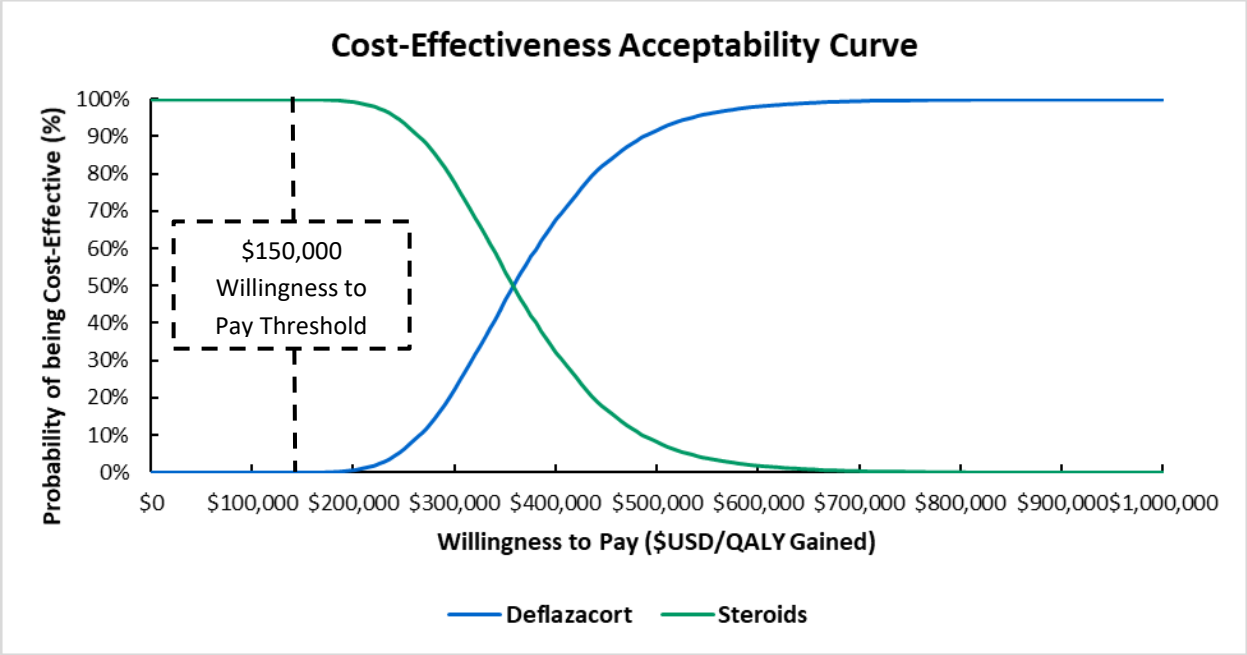


Figure E2. Probabilistic Sensitivity Analysis Results: Incremental Cost-Effectiveness Plane



The incremental cost-effectiveness plane presents each incremental cost and effect pair from the 10,000 simulations of the probabilistic sensitivity analysis. The line through the origin represents the $500,000/QALY threshold. Simulation points falling below the threshold are considered cost-effective at a $500,000/QALY gained threshold.

Figure E3. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curve



QALY: quality-adjusted life years

The blue line is a standard acceptability curve for Deflazacort relative to Prednisone (steroids) based on the probabilistic sensitivity analysis described above. The green line is its mirror image and reflects the acceptability curve for prednisone.