



Disease progression rates in ambulatory Duchenne muscular dystrophy by steroid type, patient age and functional status

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Aim: To examine benefits of corticosteroids for Duchenne muscular dystrophy (DMD) by age and disease progression. **Methods:** Data from daily steroid users (placebo-treated) were pooled from four phase 2b/3 trials in DMD. Outcomes assessed overall and among subgroups included changes from baseline to 48 weeks in six-minute walk distance (6MWD), timed function tests and North Star Ambulatory Assessment total score. **Results:** Among 231 patients receiving deflazacort ($n = 127$) or prednisone ($n = 104$), observed differences in 6MWD favoring deflazacort over prednisone were significant for patients with relatively older age (≥ 8 -years-old), greater disease progression (baseline timed stand from supine ≥ 5 s), or longer corticosteroid use (> 3 years). **Conclusion:** Daily deflazacort had greater benefits than daily prednisone particularly among older/more progressed patients.

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Duchenne muscular dystrophy (DMD) is a rare genetic disorder occurring in approximately 1 in 3600–6000 live male births [1,2], and characterized by progressive degeneration of skeletal, cardiac and pulmonary muscle fibers [3–6]. A hallmark of DMD is the loss of independent ambulation during adolescence, typically between the ages of 9 and 14 years in those treated with corticosteroids, with subsequent declines in upper limb, pulmonary and cardiac function [7–10]. There is currently no cure for DMD, and the median survival of affected patients is approximately 25–28 years in those managed with non-invasive mechanical ventilation as part of the standard of care [11–15].

Corticosteroid treatment with prednisone/prednisolone or deflazacort is the standard of care pharmacological treatment to delay disease progression in DMD [1,16]. Prednisone and its active metabolite prednisolone have been widely used for decades, although these synthetic glucocorticoids do not have a specific US FDA-approved indication for DMD. Deflazacort, an oxazoline derivative of prednisolone, was approved by the FDA in February 2017 for boys with DMD aged ≥ 5 years and the indication was later expanded to include those aged ≥ 2 years [17,18]. The risk profiles of the two corticosteroids differ, with prednisone associated with a higher risk of weight gain and deflazacort associated with a higher risk of cataracts and shorter stature, which can impact the need for dose reductions [19–22]. However, deflazacort is associated with fewer behavioral side effects, potentially due to its lower permeation of the blood-brain barrier relative to prednisone [22]. Additionally, differences in the lipid solubility of the two corticosteroids may result in differential bioavailability to muscle fibers as DMD progresses [22,23].

Both corticosteroids are considered to be “probably” or “possibly” effective in demonstrating benefit on markers of DMD progression in the latest (2016) American Academy of Neurology (AAN) guidelines [16], and have been associated with better functional outcomes, such as delayed loss of ambulation and improved strength,

motor, pulmonary, and cardiac function, as well as possibly longer survival [1,16,19,24]. Historical evidence has suggested a slight advantage of prednisone over deflazacort treatment, and the AAN classifies a greater share of evidence for prednisone as level B (“probably” effective) than level C (“possibly” effective) compared with deflazacort [16]. However, a 2016 Cochrane Review considered the quality of comparative evidence to be low [25] and more recent studies have provided stronger evidence in support of better efficacy or tolerability with deflazacort versus prednisone [22,24,26–30]. For example, deflazacort was associated with significantly slower rates of functional decline over 48 weeks than prednisone in a meta-analysis of placebo arm data from phase III trials [22,30], and a multicenter, international study found that deflazacort was associated with higher median age to reach three key DMD milestones—loss of ability to stand from supine, loss of ambulation, and loss of hand-to-mouth function—compared with prednisone [24]. Similarly, a single-center study found that deflazacort was associated with longer delay in loss of ambulation, reduced scoliosis risk, improved ambulatory function, higher share of lean body mass, shorter stature, and lower weight gain compared with prednisone [29].

Deflazacort and prednisone were most recently studied in the FOR-DMD trial, a double-blind, parallel group clinical trial conducted among 196 corticosteroid-naïve boys with DMD. Boys were aged 4–7 years at baseline and randomized to daily prednisone, daily deflazacort, or intermittent prednisone and followed for minimum of 3 years [31]. The primary outcome was a composite comprised of three end points: rise from floor velocity, forced vital capacity, and participant/parent satisfaction with treatment. While both daily corticosteroid regimens provided significant benefits over intermittent prednisone, there were no significant differences between the daily regimens for the primary outcome and its three components. Patients in both the daily and intermittent prednisone groups experienced significantly greater weight gain relative to the daily deflazacort group.

The present study aimed to investigate differences in DMD disease progression between patients treated with deflazacort versus prednisone among subgroups of patients defined by age and functional status. Similar to FOR-DMD, this study compared disease progression between ambulatory patients treated with daily regimens of the two corticosteroids. As the age distribution in the FOR-DMD trial (age 7–10 years by study end) suggests that many participants were likely in the maturational improvement phase rather than declining phase of DMD for the majority of the trial, the age subgroups of the present study were constructed to separate boys roughly according to the maturation versus the declining phases of DMD. To this end, this study pooled data from the placebo arms (i.e., with underlying corticosteroid treatment) of four DMD clinical trials and evaluated disease progression according to multiple outcomes over 48 weeks.

Materials & methods

Data source

This study used anonymized individual patient data from the placebo arms of four international clinical trials in DMD: the PTC Therapeutics phase 2b trial of ataluren (PTC 007; Clinicaltrials.gov identifier: NCT00592553) [32]; the PTC Therapeutics phase 3 trial of ataluren (Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy [ACT DMD]) (PTC 020; NCT01826487) [33]; the Eli Lilly phase 3 trial of tafamidis (Lilly; NCT01865084) [34]; and Biomarin’s phase 3 trial of drisapersen (DEMAND III; NCT01254019; provided by CureDuchenne) [35]. The sponsors of the above trials provided data to the Collaborative Trajectory Analysis Project (cTAP), which approved and facilitated the use of the data for this study.

All trials were 48 weeks in duration, and data are available on demographics, corticosteroid use, genetic testing, and several measures of ambulatory, pulmonary, and cardiac function (with some variation across datasets) (Supplementary Tables 1 & 2). Additionally, all trials required that patients were able to complete the six-minute walk distance (6MWD) test at one or more screening visits prior to randomization, typically requiring a minimum distance (e.g., 75 or 150 meters) and/or stability in assessed times (e.g., $\leq 20\%$ change between screening assessments or between screening assessment and baseline). With the exception of the PTC 007 trial, all trials required patients to have used corticosteroids for ≥ 6 months and to have been on a stable corticosteroid regimen for ≥ 3 months prior to trial entry. Together, these sources provided longitudinal, patient-level data for over 300 boys with DMD who were randomized and blinded to their treatment allocation.

As this was a post-hoc analysis of previously collected, anonymized data, no ethical review was required. All trials contributing data were previously approved by institutional human subject review boards.

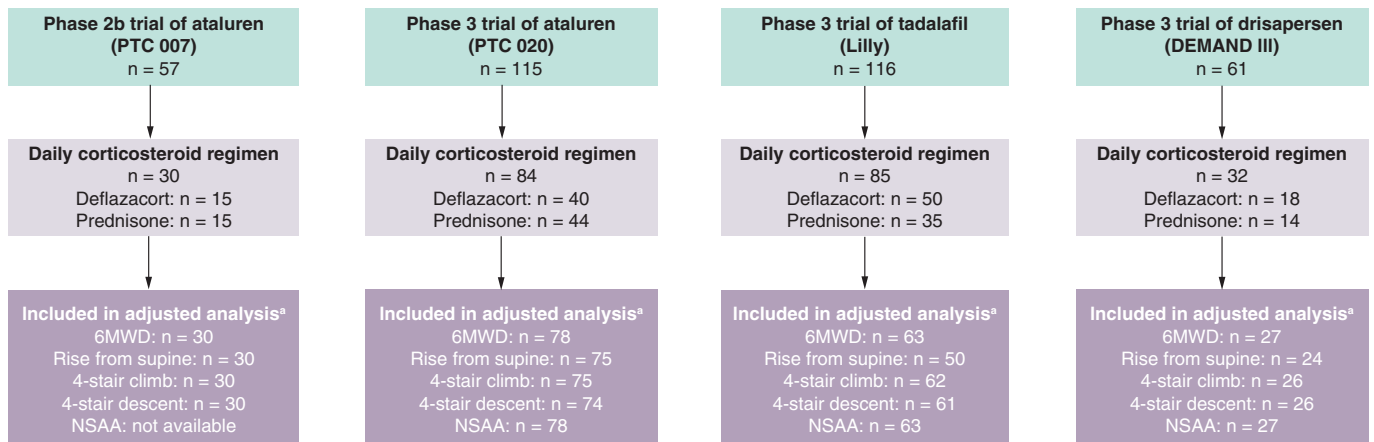


Figure 1. Sample selection within DMD clinical trial placebo arms.

^aTo be included in the adjusted analysis, patients were required to have non-missing key model covariates, baseline functional outcomes, and 48-week outcomes.

6MWD: Six-minute walk distance; DMD: Duchenne muscular dystrophy; NSAA: North Star Ambulatory Assessment.

Study population

The study sample included patients with DMD from the placebo arms of the aforementioned clinical trials who were on a daily corticosteroid regimen (either prednisone or deflazacort) at baseline. The sample sizes for the analyses described below varied based on the data collected and therefore available for analysis in the four trials. To be included in adjusted analyses of 48-week changes in outcomes, patients were required to have non-missing data on the outcome at both baseline and 48 weeks (after imputation described below), as well as non-missing data on key model covariates defined at baseline. Sample selection flowcharts for each trial are presented in [Figure 1](#).

Study measures

Patient characteristics included demographics (age, height, weight and BMI, measured with z-scores) as well as corticosteroid type (deflazacort, prednisone), duration of corticosteroid use, corticosteroid dose by weight (mg/kg), and corticosteroid dose as a percentage of the recommended dose. Outcomes included the 6MWD in meters, timed function tests (TFTs; rise from supine, 4-stair climb, and 4-stair descent in s), and the North Star Ambulatory Assessment (NSAA). For the NSAA, both the raw score (ordinal score ranging from 0–34 calculated from 17 items) and linearized score (transformation of raw score ranging from 0–100) were analyzed, with higher values of both versions representing greater functional performance and less functional impairment. The transformation of the NSAA linearized score considers that fixed (e.g., one-point) changes in ordinal levels may imply different changes in interval-level measurements.

Analyses

Imputation & truncation

Missing outcome data at the 48-week visit were imputed, as needed, using a last observation carried forward approach. Outcome data carried forward were limited to data from visits following the baseline visit and data were only carried forward up to a maximum of 12 weeks. For example, data on 6MWD from a visit in week 24 could be carried forward up to and including week 36 but no later. Based on normative values in typically developing children, TFT times below 2.5 s were truncated at 2.5 s and this truncation was performed before corresponding TFT velocities were calculated.

Baseline characteristics

Patient characteristics were summarized at baseline for the pooled sample overall and by corticosteroid type (deflazacort or prednisone). Characteristics were described in terms of demographics, corticosteroid-related characteristics, and markers of motor function (e.g., 6MWD, TFTs, NSAA). Continuous measures were summarized using means and standard deviations (SDs), while categorical/binary measures were summarized using counts and percentages.

48-week outcomes

A pooled adjusted analysis was conducted for each of the functional outcomes, with the mean change between baseline and week 48 modeled as a function of corticosteroid group, duration of previous corticosteroid use (0–3 years; and >3 years), age (≥ 4 to <8 years and ≥ 8 years), baseline rise time (≥ 5 and <5 s), baseline value of the functional measure serving as the outcome, and data source. Adjusted analyses were additionally conducted among the following subgroups of interest: age (4–8 vs >8 years), duration of corticosteroid use at baseline (0–3 vs >3 years), and timed rise from supine at baseline (≥ 5 vs <5 s).

Statistical significance & meaningful clinical change

An alpha level of 0.05 was used to determine statistical significance. The determination of clinically meaningful changes varied by outcome measure and was informed by the literature on the minimal clinically important difference from baseline: 6MWD (mean change of ≥ 28.5 m [or $\geq 8.0\%$ of mean baseline value]) [36]; TFTs ($\geq 18.9\%$ of mean baseline values) [36], and NSAA score (mean score change of 8.8 for patients on daily corticosteroid regimens) [37].

Results

Study population

A total of 231 patients receiving daily corticosteroids ($n = 127$ [deflazacort] and $n = 104$ [prednisone]) were pooled from the placebo arms of the trials and included in the adjusted analyses. The sample included 30 patients from PTC 007, 84 from PTC 020, 85 from Lilly, and 28 from DEMAND III (Figure 1).

Baseline characteristics

The mean age of the pooled sample at their baseline visit was 9.5 (SD: 2.0) years (median years [IQR]: 9.2 [8.1, 10.6]; range: 5.3–16.4); patients receiving daily deflazacort at baseline were older than those receiving prednisone (mean ages: 9.8 vs 9.1 years; $p < 0.01$) (Table 1). Weight z-score was significantly lower among patients receiving deflazacort (-0.59 [SD: 1.43]) versus prednisone (-0.19 [SD: 1.17]; $p < 0.05$), although mean absolute weights were similar between groups (30.70 [10.20] and 29.65 [8.48] kg, respectively). At their baseline visit, patients had on average 35.8 (SD: 24.4) months of steroid use (median months [IQR]: 29.3 [14.7, 52.5]; range: 3.7–112.5 months). Patients on daily deflazacort received a higher dose of deflazacort (average of 0.70 mg/kg, which is 77.3% of recommended dose of 0.9 mg/kg) than prednisone (0.55 mg/kg, which is 73.1% of the recommended dose of 0.75 mg/kg), though the difference was only statistically significant in absolute terms.

Baseline demographic characteristics by corticosteroid type within subgroups categorized by baseline age (4–8 vs >8 years), previous duration of corticosteroid use (0–3 vs >3 years), and timed rise from supine (≥ 5 vs <5 s) can be found in Supplementary Tables 3–5, respectively. Relative to younger patients, older patients were taller, heavier, had a longer history of corticosteroid use, and worse motor function. Relative to patients treated with corticosteroids for up to 3 years, patients with a longer history of corticosteroid use were older, taller, heavier, and received a lower corticosteroid dose, but had comparable motor function. Similar patterns were observed with respect to age, height, weight, and dose for patients with longer times to rise from supine relative to those with shorter times. Within each subgroup, differences between patients treated with deflazacort versus prednisone generally mirrored those observed in the overall sample, with exception of the measure used to define the subgroup.

Efficacy results among the overall daily corticosteroid population

At 48 weeks, patients on daily deflazacort experienced significantly greater preservation of function as judged by 6MWD compared with those on prednisone, with adjusted mean changes from baseline of -5.6 meters versus -43.2 meters, respectively, and a difference between groups of +37.59 (95% confidence interval [CI]: 19.29, 55.88) m ($p < 0.01$) (Figure 2). This represented a clinically meaningful loss of function (i.e., difference of ≥ 28.5 m) [36] with daily prednisone but not with daily deflazacort. Additionally, patients on daily deflazacort demonstrated significantly greater preservation of other functional outcomes over 48 weeks compared with daily prednisone, including 4-stair climb (change from baseline: 1.38 vs 3.28 s; difference between groups: -1.90 s), 4-stair descent (0.73 vs 3.08 s; -2.34 s), NSAA total score (-1.99 vs -3.55; 1.56), and NSAA linearized score (-3.70 vs -8.20; 4.50, all $p < 0.05$) (Figure 2). The difference on rise from supine between patients receiving daily deflazacort versus daily prednisone was only marginally significant over 48 weeks (2.01 vs 3.43; -1.43; $p = 0.077$). Both groups experienced clinically meaningful preservation of NSAA linearized scores (mean score change of ≤ 8.8) [37]. In contrast, only the

Table 1. Baseline characteristics for the pooled placebo arms of the DMD clinical trials who received daily corticosteroids, by corticosteroid type.

	Total (n = 231)	Deflazacort (n = 127)	Prednisone (n = 104)	p-value
Patient characteristics				
Age, years, mean $\pm$ SD	9.46 $\pm$ 1.97	9.79 $\pm$ 2.14	9.06 $\pm$ 1.65	<0.01 [‡]
Age categories, n (%)				0.05 [‡]
≥ 4 and <8 years	54 (23.38%)	23 (18.11%)	31 (29.81%)	
≥ 8 years	177 (76.62%)	104 (81.89%)	73 (70.19%)	
Height, cm, mean $\pm$ SD	124.35 $\pm$ 9.63	125.05 $\pm$ 9.82	123.50 $\pm$ 9.37	0.23
Height z-score, mean $\pm$ SD	-1.78 $\pm$ 1.21	-1.92 $\pm$ 1.25	-1.62 $\pm$ 1.16	0.06
Weight, kg, mean $\pm$ SD	30.23 $\pm$ 9.46	30.70 $\pm$ 10.20	29.65 $\pm$ 8.48	0.40
Weight z-score	-0.41 $\pm$ 1.33	-0.59 $\pm$ 1.43	-0.19 $\pm$ 1.17	<0.05 [‡]
BMI, kg/m ² , mean $\pm$ SD	19.23 $\pm$ 4.09	19.26 $\pm$ 4.42	19.18 $\pm$ 3.67	0.89
BMI z-score	0.73 $\pm$ 1.13	0.64 $\pm$ 1.15	0.85 $\pm$ 1.09	0.16
Corticosteroid information				
Corticosteroid dose, mg/kg, mean $\pm$ SD	0.63 $\pm$ 0.20	0.70 $\pm$ 0.18	0.55 $\pm$ 0.19	<0.001 [‡]
Deviation from recommended starting dose [†] , mg/kg, mean $\pm$ SD	-0.20 $\pm$ 0.18	-0.20 $\pm$ 0.18	-0.20 $\pm$ 0.19	0.92
Percent of recommended starting dose [†] , mean $\pm$ SD	75.40 $\pm$ 22.47	77.29 $\pm$ 20.18	73.09 $\pm$ 24.90	0.16
Corticosteroid duration, months, mean $\pm$ SD	35.80 $\pm$ 24.40	37.77 $\pm$ 25.44	33.39 $\pm$ 22.95	0.18
Corticosteroid duration categories, n (%)				0.58
0 to 3 years	132 (57.14%)	70 (55.12%)	62 (59.62%)	
>3 years	99 (42.86%)	57 (44.88%)	42 (40.38%)	
Motor function				
6MWD, m, mean $\pm$ SD	356.55 $\pm$ 73.43	357.77 $\pm$ 72.70	355.06 $\pm$ 74.64	0.78
Timed rise from supine, s, mean $\pm$ SD	9.10 $\pm$ 9.05	8.64 $\pm$ 8.61	9.65 $\pm$ 9.57	0.43
Timed rise from supine categories, n (%)				1.00
<5 s	86 (42.36%)	47 (42.73%)	39 (41.94%)	
≥ 5 s	117 (57.64%)	63 (57.27%)	54 (58.06%)	
Timed 4 stair climb, s, mean $\pm$ SD	6.16 $\pm$ 5.05	5.95 $\pm$ 5.33	6.42 $\pm$ 4.70	0.49
Timed 4 stair descent, s, mean $\pm$ SD	5.26 $\pm$ 5.40	4.95 $\pm$ 4.70	5.66 $\pm$ 6.17	0.34
NSAA raw score, mean $\pm$ SD	21.72 $\pm$ 7.84	22.09 $\pm$ 7.81	21.25 $\pm$ 7.89	0.45
NSAA linearized score, mean $\pm$ SD	59.69 $\pm$ 17.55	60.38 $\pm$ 17.64	58.82 $\pm$ 17.50	0.53

[†]The recommended starting dose is 0.9 mg/kg/day for deflazacort and 0.75 mg/kg/day for prednisone.
[‡]Statistically significant p-value.
6MWD: Six-minute walk distance; CI: Confidence interval; DMD: Duchenne muscular dystrophy; NSAA: North Star Ambulatory Assessment; SD: Standard deviation.

prednisone group experienced clinically meaningful declines in timed 4-stair climb (2.1–2.2 s) and neither group experienced clinically meaningful declines in timed rise from supine (3.6–3.7 s) [36].

The unadjusted differences between deflazacort and prednisone in changes in each outcome between baseline and 12, 24, 36 and 48 weeks are presented in [Supplementary Table 6](#); for most outcomes, the magnitude of the difference between groups increased over time.

Efficacy results among subgroups of the daily corticosteroid population

[Figure 3](#) & [Supplementary Table 7](#) summarize the changes in motor function outcomes from baseline to week 48 between the daily deflazacort and prednisone patients among the subgroups defined by age, corticosteroid therapy duration at baseline, and baseline timed rise from supine. Differences between patients receiving daily deflazacort versus prednisone in the change in 6MWD from baseline to 48 weeks were significant among boys who were older or with more progressed disease at baseline, including those aged ≥ 8 years (difference: +47.50 [95% CI: 26.24, 68.76] m) and those with rise from supine time ≥ 5 s (+45.11 [20.87, 69.35] m), respectively. Among those with

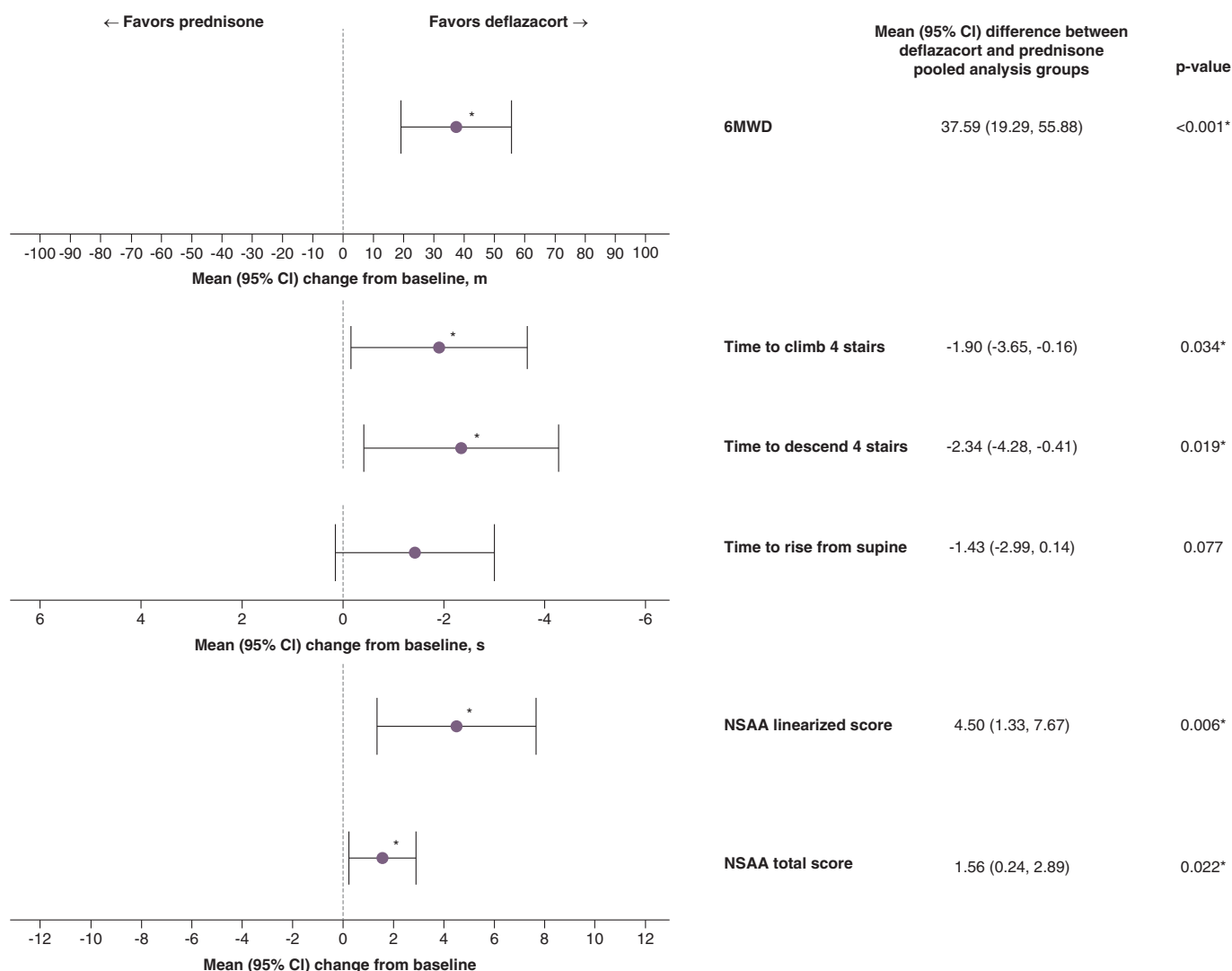


Figure 2. Comparison of change from baseline to week 48 in functional test results between the daily deflazacort and daily prednisone groups in the placebo arms of the DMD clinical trials.

6MWD: Six-minute walk distance; CI: Confidence interval; DMD: Duchenne muscular dystrophy; NSAA: North Star Ambulatory Assessment.

corticosteroid duration ≥ 3 years, differences also favored deflazacort (+56.81 [27.80, 85.82] m; all $p < 0.01$) suggesting benefits of continued steroid treatment.

Among patients aged ≥ 8 years at baseline, the differences in other end points between the daily deflazacort versus prednisone groups over 48 weeks were not significant but numerically favored deflazacort, including 4-stair climb (-2.17 s), 4-stair descent (-2.91 s; $p = 0.06$), rise from supine (-1.1 s), NSAA linearized score (+4.12), and NSAA total score (+1.70; all $p > 0.05$). There were no significant differences between corticosteroid groups in the other outcomes of these older/more advanced patients or among patients aged ≥ 4 to 8 years old, although a similar trend was observed numerically favoring deflazacort.

For patients with timed rise from supine < 5 s at baseline, there were no significant differences between daily deflazacort and prednisone over 48 weeks for all outcomes. Among patients with timed rise from supine ≥ 5 s at baseline, in addition to 6MWD, the difference between daily deflazacort and prednisone in 48-week changes was statistically significant for 4-stair descent (-3.48 s; $p = 0.046$); differences in 4-stair climb (-2.49 s), rise from supine (-2.19 s), NSAA linearized score (+4.56), and NSAA total score (+1.80) were not significant but numerically favored deflazacort.

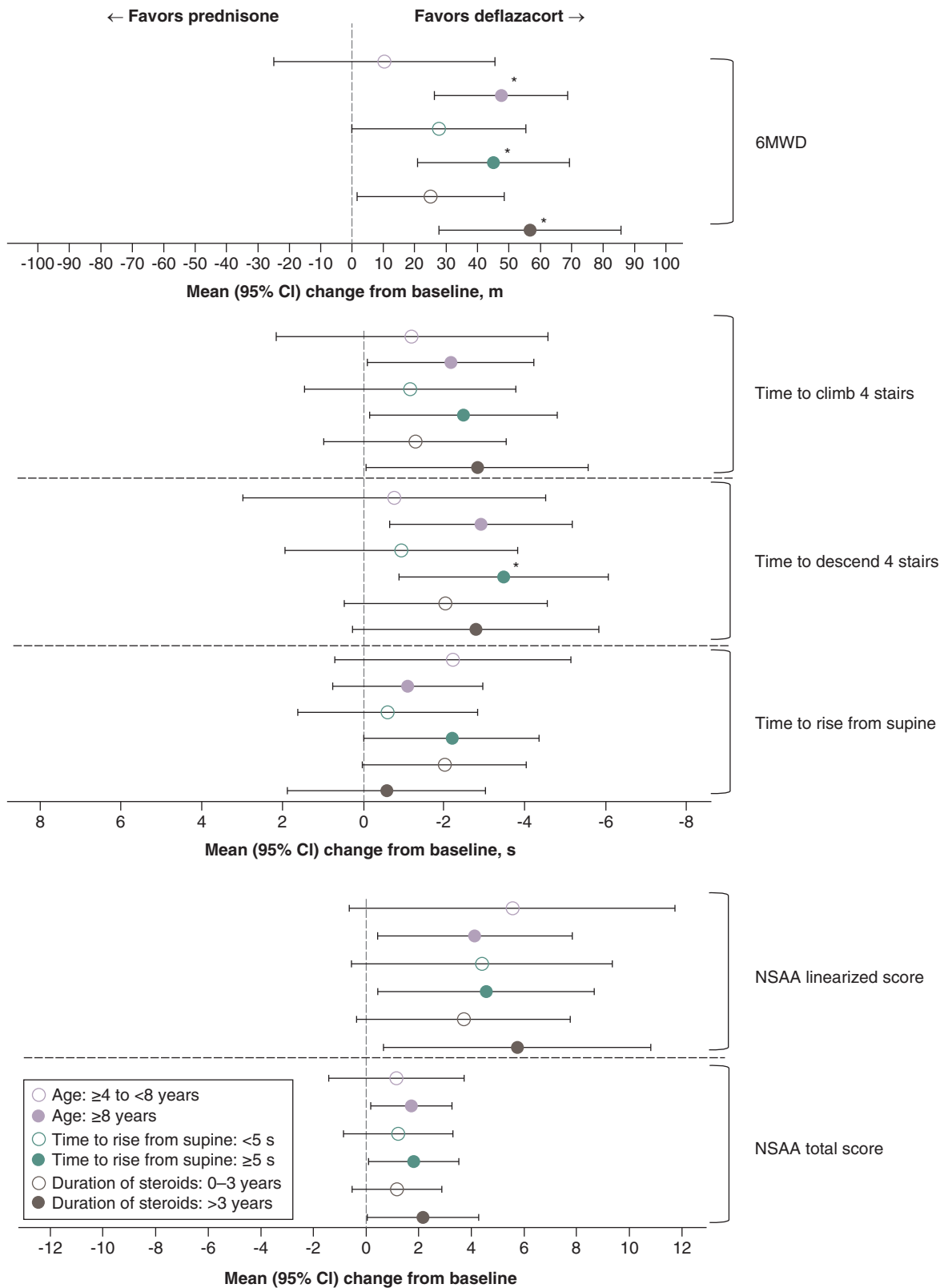


Figure 3. Comparison of change from baseline to week 48 6MWD test results between the daily deflazacort and daily prednisone groups in subgroups of the pooled DMD clinical trial placebo arms.

*Denotes statistical significance (p-value <0.05); p-values are adjusted for multiple comparisons using the Tukey method.

6MWD: Six-minute walk distance; CI: Confidence interval; DMD: Duchenne muscular dystrophy; NSAA: North Star Ambulatory Assessment.

Among patients who were on corticosteroids for 0–3 years at baseline, there were no significant differences between daily deflazacort and prednisone over 48 weeks for all outcomes, although trends numerically favored daily deflazacort. Similarly, for patients who were on corticosteroids >3 years at baseline, differences between daily deflazacort and prednisone were not statistically significant over 48 weeks but numerically favored deflazacort: 4-stair climb (-2.82 s), 4-stair descent (-2.79 s), rise from supine (-0.58 s), NSAA linearized score (+5.75), and NSAA total score (+2.16, all $p > 0.05$).

Discussion

This study assessed whether associations between steroid type and disease progression differed among subgroups of boys in the placebo arms of clinical trials of DMD therapies, particularly those who were older and/or had more advanced disease progression at baseline. The results indicated that, relative to daily prednisone, daily deflazacort was associated with greater preservation of motor function in patients with DMD after 48 weeks. The differences were more pronounced among patients who were older (i.e., aged ≥ 8 years), at a more progressed disease stage (rise from supine time ≥ 5 s at baseline), or had been on corticosteroids longer (i.e., corticosteroid use >3 years at baseline). We conclude that the potential benefits of deflazacort over prednisone, which have been previously described in several studies for broad DMD populations, may become more pronounced for older patients and for those with more progressed disease.

Although the FOR-DMD trial was “not designed to establish the equivalence of” daily deflazacort and daily prednisone regimens in DMD [31], patients on each corticosteroid regimen fared similarly with respect to the primary composite outcome. In contrast to the results of FOR-DMD, but consistent with additional recent studies, the current study observed an overall association between deflazacort and slower disease progression as measured by changes in multiple functional outcomes over 48 weeks. These findings likely reflect the fact that the patients in this study were, on average, older and more progressed at baseline compared with those enrolled in FOR-DMD, and many patients in this study were not corticosteroid-naïve. 77% of patients in this study were aged 8 years or older at baseline and 82% had been treated with corticosteroids for at least 1 year at baseline. Indeed, the magnitude of the changes in the outcomes from baseline to 48 weeks associated with the two corticosteroids were more similar in subgroups that were comparable to the FOR-DMD trial population, and more striking in subgroups differing from the FOR-DMD trial population. This, in turn, suggests that the overall results reported for the FOR-DMD trial are driven by the younger sample of boys included (4 to 8 years of age), who were both corticosteroid naïve and had less progressed disease at baseline. However, the current study was not randomized by steroid type and thus observed differences may also reflect unobserved differences in patients receiving the two corticosteroid types.

Much of the previously published evidence of differing efficacy between prednisone and deflazacort draws from comparisons in patients ages 7 years and older who have baseline clinical assessments predictive of clinical deterioration [22,24,29,30]. Differences are likely due to biologic properties of the compounds such as lipid solubility [26] and/or differences in tolerability driving dose reductions. Given the wealth of published data favoring deflazacort in older more disease progressed patients and since patients older than 10 years who are either ambulatory or non-ambulatory and in the decline phase of the disease were not studied, results of FOR-DMD cannot necessarily be extrapolated to those populations.

The design and results of this study are comparable to those of a prior meta-analysis of placebo-arm data from clinical trials in DMD by McDonald *et al.* [22]. That meta-analysis used data from two of the four trials used in this analysis and also compared 48-week changes in outcomes between deflazacort and prednisone (according to any regimen) and similarly observed that treatment with deflazacort was associated with slower functional declines than with prednisone. The present analysis is limited to patients on daily regimens, and for some outcomes, the results indicated differences of larger magnitudes. For example, deflazacort was associated with preservation of +37.6 m in 6MWD (versus +28.3 m in McDonald *et al.*) and +4.5 points on NSAA linearized score (versus +2.9 points) at 48 weeks. The sample of the present study was also drawn from four trials instead of two, its larger sample size allowing for exploration of heterogeneity along other dimensions (e.g., age, severity, steroid duration).

The results of this study should be considered in the context of several important limitations. First, as this study only compared daily corticosteroid regimens over 48 weeks, the findings cannot be applied to different regimens (e.g., every other day or high dose weekend) or results over longer time horizons. Second, when pooling data, the data sources had some differences in terms of inclusion/exclusion criteria, trial size, and the availability of data elements. For example, both PTC trials were limited to patients with nonsense mutations, which may influence the results to the extent that there is effect modification of the relationship between steroid type and disease progression

by DMD genotype, of which we are not currently aware. In addition, NSAA data were unavailable in PTC 007, which may have limited the power to detect significant differences in the subgroup analyses for that outcome. Finally, the PTC 020 and Lilly trials were the largest of the four trials, and our aggregate results may be more representative of their patient populations relative to PTC 007 and DEMAND III. Third, corticosteroid classification was based on the corticosteroid regimen at baseline and did not consider steroid switching and/or discontinuation. However, switching and discontinuation were extremely rare events in the four trials, and three of the four trials mentioned in their inclusion criteria that there was a “reasonable expectation” that corticosteroid dosing and regimen would not change substantially over the course of the study, with the exception of weight-related adjustments. Fourth, as this was a comparison of non-randomized treatment groups, there was the possibility of residual confounding due to unobserved differences between patients receiving deflazacort and prednisone. Such unobserved differences may include clinical characteristics of patients, which could impact both the choice to prescribe deflazacort or prednisone and eventual treatment outcomes. Additionally, patients who are taking deflazacort in the US may have greater access to other standard of care management strategies through their insurance and available resources. Further research on steroid differences by geographic region would be helpful in quantifying this potential bias. Finally, this study did not evaluate adverse effects or side effects associated with the corticosteroids, although future analyses focused on this would be useful.

Conclusion

Overall, these results add to the body of evidence comparing deflazacort to prednisone across clinically meaningful subgroups of patients with DMD. Specifically, the results are consistent with a significant benefit of daily deflazacort compared with daily prednisone as assessed by functional outcome measures such as 6MWD, TFTs, and NSAA score. The results favored deflazacort over prednisone in all subgroups, but to a greater extent in subgroups of patients who were older, had more advanced disease progression, and had received corticosteroids for a longer duration.

Summary points

- Corticosteroid treatment with prednisone/prednisolone or deflazacort is the standard of care pharmacological treatment for Duchenne muscular dystrophy (DMD).
- The extent of the benefits of corticosteroids for DMD may vary by patient age and functional status.
- The present study investigated differences in DMD disease progression between patients treated with deflazacort versus prednisone among subgroups of patients defined by age, functional status, and duration of previous corticosteroid use.
- Data were pooled from the placebo arms of four phase 2b/3 trials; 231 patients with DMD who were on daily deflazacort (n = 127) or prednisone (n = 104) at baseline were included.
- After 48 weeks of treatment, daily deflazacort was associated with significantly greater preservation of motor function in patients with DMD, as assessed by six-minute walk distance, timed function tests and North Star Ambulatory Assessment scores.
- The differences were more pronounced among subgroup of patients who were older (i.e., aged ≥ 8 years), at a more progressed disease stage (i.e., rise from supine time ≥ 5 s at baseline), or had been on corticosteroids longer (i.e., corticosteroid use >3 years at baseline).
- The findings demonstrate a significant benefit of daily deflazacort compared with daily prednisone in DMD, particularly among older patients and those with more progressed disease and longer corticosteroid use.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0190>

Author contributions

JR Marden, H Lane, A Zhang, H Nguyen, M Frean and J Signorovitch contributed to study conception and design, collection and assembly of data, and data analysis and interpretation. CM McDonald, PB Shieh, BL Wong, P Trifillis and K Koladicz contributed to study conception and design and data interpretation. All authors reviewed and approved the final content of this manuscript.

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Ethical conduct of research

This was a post-hoc analysis of previously collected, anonymized trial data; thus, no ethical review was required.

Data sharing statement

This publication is based on research using data from data contributors CureDuchenne that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication. Data were also provided to the authors by PTC Therapeutics (placebo arms from ataluren trials) and by Eli Lilly via the Collaborative Trajectory Analysis Project (cTAP) (tadalafil DMD trial). Enquiries regarding data access can be made to PTC Therapeutics, Trancelerate (<https://www.transceleratebiopharmainc.com/>) and Vivli (<https://vivli.org/>).

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Birnkrant DJ, Bushby K, Bann CM *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* 17(3), 251–267 (2018).
2. Bushby K, Finkel R, Birnkrant DJ *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 9(1), 77–93 (2010).
3. Chung J, Smith AL, Hughes SC *et al.* Twenty-year follow-up of newborn screening for patients with muscular dystrophy. *Muscle Nerve* doi:10.1002/mus.24880 (2015).
4. Romitti PA, Zhu Y, Puzhankara S *et al.* Prevalence of Duchenne and Becker muscular dystrophies in the United States. *Pediatrics* 135(3), 513–521 (2015).
5. Mendell JR, Shilling C, Leslie ND *et al.* Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann. Neurol.* 71(3), 304–313 (2012).
6. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifirò G. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet J. Rare Dis.* 15(1), 141 (2020).

7. Ricotti V, Ridout DA, Scott E *et al.* Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *J. Neurol. Neurosurg. Psych.* 84(6), 698–705 (2013).
8. Pane M, Fanelli L, Mazzone ES *et al.* Benefits of glucocorticoids in non-ambulant boys/men with Duchenne muscular dystrophy: a multicentric longitudinal study using the Performance of Upper Limb test. *Neuromuscul. Disord.* 25(10), 749–753 (2015).
9. Mazzone E, Bianco F, Main M *et al.* Six minute walk test in type III spinal muscular atrophy: a 12-month longitudinal study. *Neuromuscul. Disord.* 23(8), 624–628 (2013).
10. Seferian AM, Moraux A, Annoussamy M *et al.* Upper limb strength and function changes during a one-year follow-up in non-ambulant patients with Duchenne muscular dystrophy: an observational multicenter trial. *PLOS ONE* 10(2), e0113999 (2015).
11. Ishikawa Y, Miura T, Ishikawa Y *et al.* Duchenne muscular dystrophy: survival by cardio-respiratory interventions. *Neuromuscul. Disord.* 21(1), 47–51 (2011).
12. Lomauro A, D'angelo MG, Aliverti A. Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. *Ther. Clin. Risk Manag.* 11, 1475–1488 (2015).
13. Rall S, Grimm T. Survival in Duchenne muscular dystrophy. *Acta Myol.* 31(2), 117–120 (2012).
14. Passamano L, Taglia A, Palladino A *et al.* Improvement of survival in Duchenne muscular dystrophy: retrospective analysis of 835 patients. *Acta Myol.* 31(2), 121–125 (2012).
15. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in Duchenne muscular dystrophy: reproduced individual patient data meta-analysis. *Neurology* 97(23), e2304–e2314 (2021).
16. Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 86(5), 465–472 (2016).
17. Highlights of prescribing information: EMFLAZA (deflazacort) (2017).
www.accessdata.fda.gov/drugsatfda_docs/label/2017/208684s000,208685s000lbl.pdf (Accessed January 25, 2022).
18. Highlights of prescribing information: EMFLAZA (deflazacort) (2019).
www.accessdata.fda.gov/drugsatfda_docs/label/2019/208684s003,208685s003lbl.pdf (Accessed February 24, 2022).
19. Griggs RC, Miller JP, Greenberg CR *et al.* Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurology* 87(20), 2123–2131 (2016).
20. Rice ML, Wong B, Horn PS, Yang MB. Cataract development associated with long-term glucocorticoid therapy in Duchenne muscular dystrophy patients. *J. AAPOS* 22(3), 192–196 (2018).
21. Lamb MM, West NA, Ouyang L *et al.* Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. *J. Pediatrics* 173, 207–213.e203 (2016).
22. McDonald CM, Sajeev G, Yao Z *et al.* Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: a meta-analysis of disease progression rates in recent multicenter clinical trials. *Muscle Nerve* 61(1), 26–35 (2020).
- **Meta-analysis characterizing disease progression over 48 weeks among boys receiving deflazacort vs prednisone/prednisolone placebo arm treatment in the tadalafil Duchenne muscular dystrophy (DMD) trial and the Ataluren Confirmatory Trial in DMD (ACT DMD).**
23. Assandri A, Buniva G, Martinelli E, Perazzi A, Zerilli L. Pharmacokinetics and metabolism of deflazacort in the rat, dog, monkey and man. *Adv. Exp. Med. Biol.* 171, 9–23 (1984).
24. McDonald CM, Henricson EK, Abresch RT *et al.* Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet* 391(10119), 451–461 (2018).
25. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst. Rev.* 2016(5), CD003725 (2016).
26. Biggar WD, Skalsky A, McDonald CM. Comparing deflazacort and prednisone in Duchenne muscular dystrophy. *J. Neuromuscul. Dis.* 9(4), 463–476 (2022).
- **Review of deflazacort and prednisone/prednisolone regarding key pharmacological features, relative efficacy, and safety profiles in patients with DMD based on evidence from randomized clinical trials, prospective studies, meta-analyses, and post-hoc analyses.**
27. Marden JR, Santos C, Pfister B *et al.* Steroid switching in dystrophinopathy treatment: a US chart review of patient characteristics and clinical outcomes. *J. Comp. Eff. Res.* 10(14), 1065–1078 (2021).
- **Retrospective chart review study describing reasons for switching from prednisone/prednisolone to deflazacort and associated clinical outcomes among patients with Duchenne and Becker muscular dystrophy.**
28. Shieh PB, McIntosh J, Jin F *et al.* Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: a post HOC analysis from the ACT DMD trial. *Muscle Nerve* 58(5), 639–645 (2018).
- **Post hoc analysis of the placebo arm of the ACT DMD trial comparing the efficacy and safety of deflazacort versus prednisone/prednisolone in slowing DMD disease progression.**

29. Marden JR, Freimark J, Yao Z, Signorovitch J, Tian C, Wong BL. Real-world outcomes of long-term prednisone and deflazacort use in patients with Duchenne muscular dystrophy: experience at a single, large care center. *J. Comp. Eff. Res.* 9(3), 177–189 (2020).
 - **Retrospective single-center study assessing ambulatory, pulmonary, cardiac, growth and bone-health outcomes among 435 boys with DMD receiving deflazacort or prednisone in real-world practice.**
30. Shieh PB, Elfring G, Trifillis P *et al.* Meta-analyses of deflazacort versus prednisone/prednisolone in patients with nonsense mutation Duchenne muscular dystrophy. *J. Comp. Eff. Res.* 10(18), 1337–1347 (2021).
31. Guglieri M, Bushby K, McDermott MP *et al.* Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy: a randomized clinical trial. *JAMA* 327(15), 1456–1468 (2022).
 - **Double-blind, parallel-group randomized trial evaluating the long-term efficacy and adverse effects of daily prednisone, daily deflazacort, and intermittent prednisone in 196 corticosteroids-naïve boys with DMD.**
32. Bushby K, Finkel R, Wong B *et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve* 50(4), 477–487 (2014).
33. McDonald CM, Campbell C, Torricelli RE *et al.* Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 390(10101), 1489–1498 (2017).
34. Victor RG, Sweeney HL, Finkel R *et al.* A phase 3 randomized placebo-controlled trial of tadalafil for Duchenne muscular dystrophy. *Neurology* 89(17), 1811–1820 (2017).
35. Goemans N, Mercuri E, Belousova E *et al.* A randomized placebo-controlled phase 3 trial of an antisense oligonucleotide, drisapersen, in Duchenne muscular dystrophy. *Neuromuscul. Disord.* 28(1), 4–15 (2018).
36. McDonald CM, Henricson EK, Abresch RT *et al.* The 6-minute walk test and other clinical endpoints in Duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. *Muscle Nerve* 48(3), 357–368 (2013).
37. Mayhew AG, Cano SJ, Scott E *et al.* Detecting meaningful change using the North Star Ambulatory Assessment in Duchenne muscular dystrophy. *Dev. Med. Child Neurol.* 55(11), 1046–1052 (2013).