Meta-analyses of Deflazacort in Patients With Nonsense Mutation Duchenne Muscular Dystrophy

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1. Introduction

- Duchenne muscular dystrophy (DMD) is a rare and fatal X-linked disorder that affects 1 in every 3600-6000 live male births and is characterized by progressive muscle weakness and decline in function.[1,2]
- The current standard of care for DMD includes therapy with prednisone, prednisolone, or deflazacort;[3] these agents can slow the decline in muscle strength and motor function and may delay loss of ambulation (LoA).[2,4,5]
- All patients enrolled in the ACT DMD study were on corticosteroid therapy (deflazacort or prednisone/prednisolone) for ≥6 months at study entry and were expected to maintain a stable dose and regimen during the study unless the dose was being adjusted for weight change.[6] Patients in the phase 2b trial who were receiving corticosteroid therapy at study entry were required to remain on a stable dose throughout the trial; 71% of these patients were using corticosteroids.[7]
- Meta-analyses are useful for estimating treatment effects for agents used to treat diseases that are rare and have a heterogeneous course of progression; these analyses contain sample sizes sufficient for overcoming confounding influences of patient subgroups.[8]
- We conducted these post-hoc meta-analyses using placebo arms of the phase 2b and ACT DMD trials to assess evidence for the efficacy of deflazacort or prednisone/prednisolone for slowing disease progression in patients with nmDMD.

2. Methods

- The first meta-analysis used data from the intent-to-treat (ITT) population of the phase 2b and ACT DMD trials who were randomized to placebo; the patients included from the phase 2b trial were limited to those who met the entrance criteria for the ACT DMD trial (aged ≥7 years and ≤16 years, diagnosed with nmDMD, with a baseline 6MWD both ≥150 m and ≤80% of that predicted for age and height and receiving concomitant corticosteroid therapy).
- The second analyses (300 to <400 m) used a subgroup of patients from the first meta-analysis who had a baseline 6MWD ≥300 m and <400 m. This is the subgroup where a drug effect can be observed in a 1-year trial using 6MWT as an endpoint.
- The third analyses (<400) used a subgroup of patients from the first meta-analysis who had a baseline 6MWD <400 m. Patients with baselines <400 m are expected to show decline in their walking ability within a 1-year study while those with >400 m are likely to remain stable.
- All meta-analyses evaluated the following efficacy endpoints that were included in both trials:
  - Change in 6MWD from baseline to week 48 (primary endpoint in both trials)
  - Change from baseline to week 48 in timed function tests (TFTs) 10 m walk/run; 4-stair climb and 4-stair descend,
- Safety parameters, including adverse events (AEs) were assessed throughout both trials.
- A fixed-effects model was used, whereby the point estimate was given a weight equal to the inverse of the variance of the point estimate for each study.

3. Results

Demographics

- Baseline characteristics were well balanced in both trials.
- In the phase 2b trial, no patients discontinued because of an adverse event. In the ACT DMD trial, 1 patient randomized to placebo discontinued owing to an adverse event (disease progression).

Table 1. Baseline patient demographics and characteristics by study

	Phase 2b		ACT DMD	
Characteristic	**Deflazacort (n = 17)**	**Prednisone/ prednisolone (n = 23)**	**Deflazacort (n = 53)**	**Prednisone/ prednisolone (n = 61)**
Age, y				
Mean (SD)	9.1 (2.91)	8.3 (1.5)	9.2 (1.7)	8.8 (1.6)
Range	6, 15	5, 11	7, 14	7,13
Age group, n (%)				
<9 y	8 (47.6)	12 (52.2)	23 (43.4)	30 (49.2)
≥9 y	9 (52.9)	11 (47.8)	30 (56.6)	31 (50.8)
Race, n (%)				
White	16 (94.1)	22 (95.7)	46 (86.8)	40 (63.9)
Black/African Amer.	0 (0)	0 (0)	0 (0.0)	1 (1.6)
Asian	1 (5.9)	0 (0)	4 (7.5)	2 (3.3)
Hispanic	0 (0)	(0)	3 (5.7)	5 (8.2)
Other	0 (0)	1 (4.3)	0 (0.0)	4 (6.6)
Missing	(0)	0 (0)	0 (0.0)	10 (16.4)
Weight, kg				
Mean (SD)	29.89 (9.9)	30.95 (9.2)	30.9 (11.9)	30.5 (9.2)
Range	17.9, 50.1	19.2, 54.6	18.1, 68.0	18.2, 59.8
Height, cm				
Mean (SD)	123.06 (0.2)	124.25 (10.4)	127.0 (10.6)	125.7 (10.4)
Range	106.0, 141.0	107.0, 148.0	106.7, 148.7	101.8, 151.0
BMI, kg/m^2				
Mean (SD)	19.2 (4.2)	19.7 (3.4)	18.6 (4.7)	19.0 (3.5)
Range	14.1, 28. 6	14.0, 25.6	13.0, 36.0	13.1, 27.1
Corticosteroid use prior to baseline, n(%)				
6 to <12 months	1 (5.9)	5 (21.7)	7 (13.2)	11 (18.0)
≥12 months	16 (94.1)	18 (78.3)	46 (86.8)	50 (82.0)

Dosing

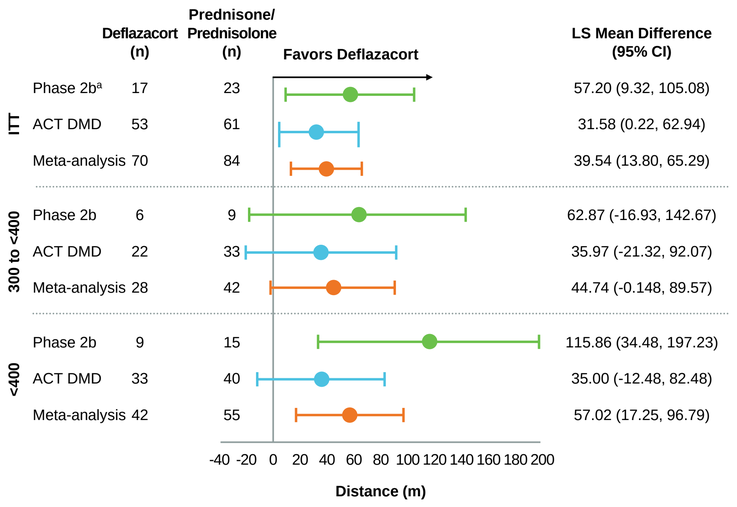
- Daily dosing was the most common dosing regimen for either deflazacort or prednisone/prednisolone
- Mean daily deflazacort doses were 0.785 mg/kg in the Phase 2b trial and 0.695 mg/kg in ACT DMD.
- Mean daily prednisone/prednisolone doses were 0.684 mg/kg in the Phase 2b trial and 0.61 mg/kg in ACT DMD.

(continued)

3. Results (continued)

Figure 1. Change from baseline to week 48 in 6MWD*

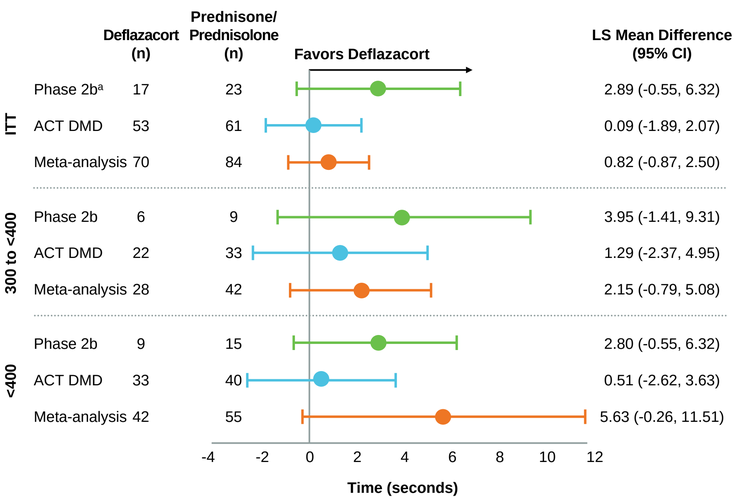
- For the ITT populations, treatment differences were significant in favor of deflazacort versus prednisone/prednisolone.
  - Phase 2b trial: LS mean difference of 57.20 m (95% CI, 9.32 to 105.08); *P*=0.021
  - ACT DMD: 31.58 m (0.22 to 62.94); *P*=0.048
- Meta-analysis: 39.54 m (13.799 to 65.286); *P*=0.003
- Differences were noted between deflazacort and prednisone/prednisolone in the 300 m to <400 m subgroup but were not significant
- The treatment differences between deflazacort and prednisone/prednisolone for the <400 population in the Phase 2b trial (115.86 m) and in the meta-analysis (57.02) were significant
  - Phase 2b trial: 115.86 m (34.98 to 197.23); *P*=0.008
  - Meta-analysis: 57.02 m (17.25 to 96.79); *P*=0.0049



* Data shown are least-square mean treatment differences between deflazacort and prednisone/prednisolone and 95% confidence intervals.
300 to <400, patients with a 6-minute walk distance ≥300 m and <400 m at baseline; <400, patients with a 6-minute walk distance <400 m at baseline; 6MWD, 6-minute walk distance; ITT, intent-to-treat.
[a] ITT population that met ACT DMD entry criteria.

Figure 2. Change from baseline to week 48 in 10 m walk/run

- Several of the treatment differences favored deflazacort over prednisone/prednisolone for the Phase 2b trial, ACT DMD, and in the meta-analysis. However, none of the differences were significant.



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300 to <400, patients with a 6-minute walk distance ≥300 m and <400 m at baseline; <400, patients with a 6-minute walk distance <400 m at baseline; 6MWD, 10 m walk/run, time to walk or run 10 m; ITT, intent-to-treat.
[a] ITT population that met ACT DMD entry criteria

Figure 3. Change from baseline to week 48 in the 4-stair climb*

- In the ITT population, treatment differences favored deflazacort over prednisone/prednisolone in the phase 2b trial, and the differences were significant in ACT DMD.
  - ACT DMD : -2.88 sec (-5.27 to -0.48); *P*=0.02
  - Meta-analysis: -2.73 sec (-4.70 to -0.72); *P*=0.008
- No significant differences were noted between either corticosteroid in the 300m to <400m subgroup
- For the <400 population, treatment differences favored deflazacort versus prednisone/prednisolone; the difference was significant for the ACT DMD trial and the meta-analysis.
  - ACT DMD: -4.65 sec (-8.45 to -0.85); *P*=0.017
  - Meta-analysis: -4.16 sec (-7.51 to -0.81); *P*=0.015

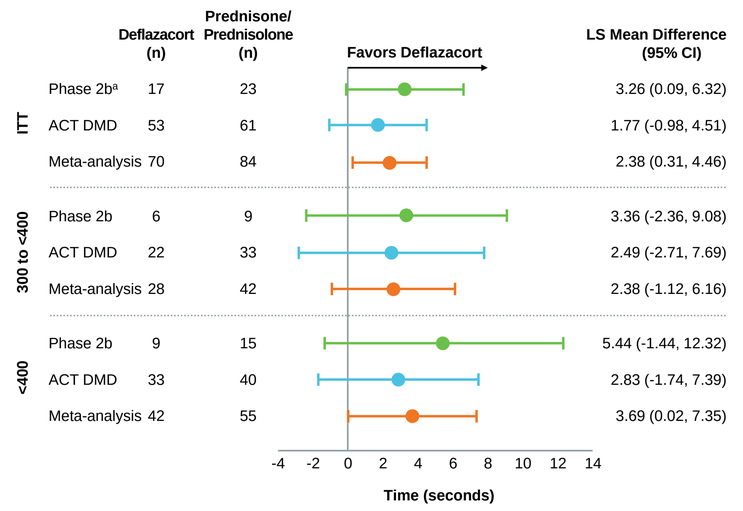
* Data shown are least-square mean treatment differences between deflazacort and prednisone/prednisolone and 95% confidence intervals.
300 to <400, patients with a 6-minute walk distance ≥300 m and <400 m at baseline; <400, patients with a 6-minute walk distance <400 m at baseline; 4-stair climb, time to climb 4 stairs; ITT, intent-to-treat.
[a] ITT population that met ACT DMD entry criteria.

(continued)

3. Results (continued)

Figure 4. Change from baseline to week 48 in 4-stair descend*

- For the ITT population, the treatment difference favored deflazacort in the meta-analysis (-2.38 sec [-4.62 to -0.31]; *P*=0.02).
- Treatment differences for the <400 population favored deflazacort: -3.69 sec (-7.53 to -0.019); *P*=0.05



* Data shown are least-square mean treatment differences between deflazacort and prednisone/prednisolone and 95% confidence intervals.
300 to <400, patients with a 6-minute walk distance ≥300 m and <400 m at baseline; <400, patients with a 6-minute walk distance <400 m at baseline; 6MWD, 4-stair descend, time to descend 4 stairs; ITT, intent-to-treat.
[a] ITT population that met ACT DMD entry criteria.

Safety

- The five most frequent adverse events observed among patients treated with deflazacort in the meta-analysis (n=70) were: vomiting (n=18, 26%), headache (n=15, 21%), nasopharyngitis (n=11, 16%), pain in extremity (n=9, 13%), and cough (n=9, 13%).
- The five most frequent adverse events observed among patients treated with prednisone/prednisolone in the meta-analysis (n=85) were: pain in abdomen (n=21, 25%), nasopharyngitis (n=20, 24%), headache (n=18, 23%), vomiting (n=16, 19%), pyrexia (n=14, 16%).

4. CONCLUSIONS

- These meta-analyses demonstrate that patients who received deflazacort benefited in terms of ambulation and two of the three timed function tests as compared with those who received prednisone/prednisolone.
- Meta-analyses of similar trials allow a more robust estimate of the true effect size than individual trials; these two trials had similar designs, and no relevant trials were excluded from the meta-analyses.
- Deflazacort and prednisone/prednisolone were generally well tolerated by patients with nmDMD. Adverse event profiles were generally similar among patients who received deflazacort and those who received prednisone/prednisolone. The spectrum and severity of AEs were consistent across the trials.

Disclosures

EO, GE, PT, JM, and CS are employees of PTC Therapeutics.

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