CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	208684 & 208685
Drug Name:	EMFLAZA™ (Deflazacort)
Indication(s):	Duchenne muscular dystrophy (DMD)
Applicant:	Marathon Pharmaceuticals, LLC
Date(s):	Submission date: 06/09/2016
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1 EXECUTIVE SUMMARY

This is the statistical review of the Marathon Pharmaceuticals' application for the approval of the investigational drug EMFLAZA™ (deflazacort). The submitted data overall provide statistical evidence to support the efficacy of deflazacort in Duchenne muscular dystrophy (DMD) subjects.

The primary efficacy analysis from the pivotal study NM-001 demonstrated a statistically significant difference in change in muscle strength score from Baseline to Week 12 in favor of the two deflazacort groups (0.9 mg/kg/day: p = 0.0173; 1.2 mg/kg/day: p = 0.0003) and the prednisone group (p = 0.0002) compared to the placebo. The treatment effect is consistent among the age subgroups.

Supportive trial NM-002 was for a long-term treatment effect of deflazacort compared to the placebo. The analysis result of the change in muscle strength score at Year 2 (the primary time point) was not statistically significant, although it showed numerical trend favoring deflazacort. The analysis of Year 2 data was not conclusive because of the high percentage (about 50%) of missing data. The amount of missing data at Year 1 is limited, and the treatment effects in muscle strength score at Month 6 and Year 1 were nominally significant.

2 INTRODUCTION

2.1 Overview

The primary pivotal clinical study, Study NM-001, was to establish the effectiveness of deflazacort. The trial was [redacted] (b) (4) completed by the study investigators. The final data summary and clinical study report were completed by Marathon Pharmaceuticals, LLC. Marathon has also licensed data from a supporting pivotal clinical study, Study NM-002.

Both studies were randomized, double-blind, placebo-controlled studies conducted in patients with DMD. The study NM-001 evaluated two doses of deflazacort, 0.9 mg/kg/day and 1.2 mg/kg/day. In Study NM-002 an alternate deflazacort dosing regimen (i.e., 2 mg/kg once every 2 days) was investigated. Both studies assessed changes in muscle strength score as the primary efficacy endpoint, however, each study used a different assessment index for muscle strength. Study NM-001 evaluated the change in muscle strength score from Baseline to Week 12 using an 11 point modified version of the Medical Research Council (MRC) scale taking the mean of 34 strength measurements into consideration, while Study NM-002 evaluated the change in muscle strength from Baseline to 2-years or loss of ambulation (whichever occurred first) using a 0 to 5 point scale converted to an MRC index score expressed as a percentage of "normal strength" for the sum of four strength measurements.

Table 1: **Summary of Studies**

Study	Study Design	Population	Deflazacort Dosage	Number of Subjects
MP-104-NM-001	Multicenter, randomized, double-blind, placebo- and active-controlled, parallel group	Male children aged 5 to 15 years with Duchenne or Becker muscular dystrophy with documented proof of mutation of the dystrophin gene, onset of weakness before 5 years of age, and increased serum creatinine kinase activity at least 10x upper limit of normal at some stage in their illness.	0.9 mg/kg daily or 1.2 mg/kg daily	196 (51 received deflazacort 0.9 mg/kg daily and 49 received deflazacort 1.2 mg/kg daily)
MP-104-NM-002	Multicenter, randomized, double-blind, placebo-controlled, parallel group.	Ambulatory male children aged 5 to 11 years old (at study enrollment) with documented symptoms onset prior to the age of 5 years with diagnosis confirmed by: neurological examination, electromyography, serum exams or muscle biopsy.	2 mg/kg once every 2 days	31 (20 on deflazacort)

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, which are located in the following directory: \\cdsesub1\evsprod\NDA208684\0000\m5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

For the pivotal Study NM-001, all source data were sent to (b) (4) for entry into a SAS database. Original CRF books were then destroyed in 6 sites and a total of 56 of 196 (28.6%) original completed CRF books were located and retrieved. As a result, some variables not entered into the database (such as subject disposition) were not available for all patients. Additionally, data discrepancies could not be resolved due to missing source document. Patient level data related to the efficacy measures were available.

Both studies were conducted more than 20 years ago. The statistical analysis plans (SAP) for the available data were drafted by Marathon in 2015. The analyses methods stated in the SAP for

Study NM-001 were deviated from those pre-specified in the protocol (see section 3.2.1.2 of this review).

3.2 Evaluation of Efficacy

3.2.1 Study NM-001

3.2.1.1 Study Design and Endpoints

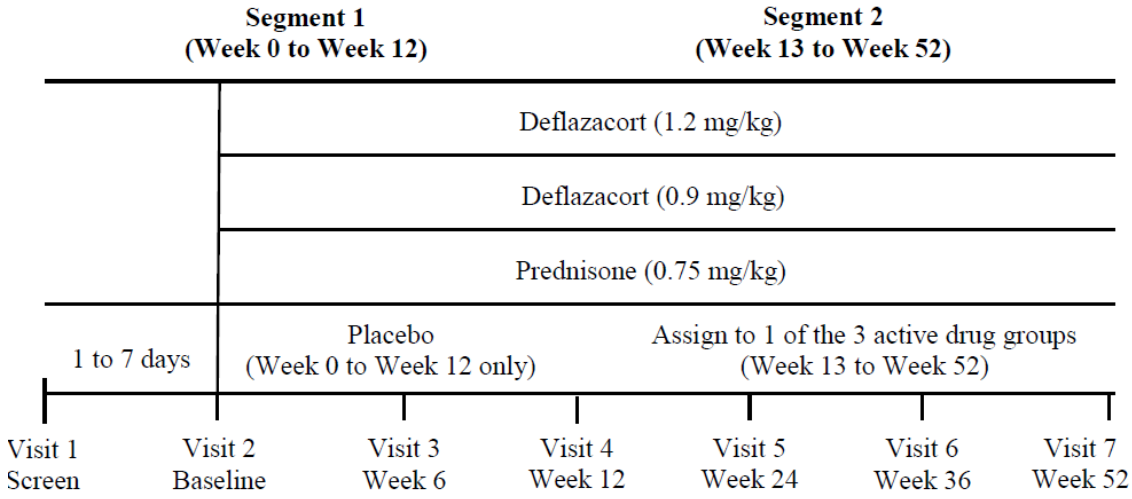
The original sponsor of the Study NM-001was (b) (4) Marathon completed the data analysis and issued the clinical study report after the original sponsor transferred rights of the study to the primary investigators and the US IND to Dr. Fenichel at Vanderbilt University.

The study was conducted in 4 centers in the US and 5 centers in Canada. The first patient was enrolled on April 26, 1993 and the study was completed on April 20, 1995. The protocol was finalized on December 18, 1992 with a description of statistical analyses. The SAP for the available data was drafted by Marathon and finalized on January 19, 2015. Analyses issues in the SAP that suggest changes to the principal features stated in the protocol are discussed in this review.

Study Design

This is a double-blind, randomized, multicenter study of 180 boys (planned) with Duchenne/Becker muscular dystrophy aged 5 to 15 years. At screening, eligible patients were randomly assigned to 4 treatment groups in a 1:1:1:1 ratio to deflazacort (0.9 or 1.2 mg/kg/day) or prednisone (0.75 mg/kg/day) or placebo. Randomization was stratified by center and by whether the patient was classified as ambulatory or nonambulatory (leg-function grade 1- 7 vs 8-10). In Segment 1, deflazacort and prednisone were compared with placebo for the first 12 weeks of treatment following Baseline. In Segment 2, placebo patients were re-randomized to one of three active treatment groups. Patients originally randomized to prednisone or one of the two deflazacort arms continued in that study arm for an additional 40 weeks (Figure 1).

Figure 1. Overview of Study NM-001



Efficacy Endpoints

The primary efficacy variable is the change in average muscle strength score from baseline to Week 12. Patients were asked to perform specific muscle strength assessments in various positions and each test was graded using an 11-point scale.

The key secondary endpoint as specified in the protocol is not clear. The protocol specified the following secondary endpoints in section 5.1, "Parameters Subject to Analysis":

- change in average muscle strength score from 12 weeks to end of study
- change in myometric measurements
- timed functional tests including pulmonary function tests
- muscle metabolic markers
- physician global assessment

However, the secondary study objective stated in the protocol is "to assess the efficacy of deflazacort versus prednisone over a 52-week period of treatment." In addition, section 5.3 of the protocol specified the null hypotheses which are to be tested in a confirmatory sense at 2-sided 5% level of significance are the following:

Ho $_1$: There is no difference between deflazacort, prednisone and placebo with respect to change in average muscle strength score for patients treated at up to 12 weeks.

Ho $_2$: There is no difference between deflazacort and prednisone with respect to change in average muscle strength score for patients treated at up to 52 weeks.

The applicant's interpretation of the specified secondary endpoints, as stated in the SAP, is the following: "the change in average muscle strength score from Week 12 to Week 52 is a secondary efficacy endpoint and the change from baseline to Week 52 (including only subjects randomized to active treatment in Segment I) is an exploratory endpoint."

However, this reviewer considered "the change in average muscle strength score from baseline to Week 52" to be the key secondary endpoint for the following reasons:

1. The description of the study objective, the null hypotheses, and the statistical methodology for the secondary endpoints in the protocol all used the wording "up to 52 weeks" or "after 52 weeks of treatment" and didn't mention Week 12. Change from Week 12 to Week 52 is only mentioned in the section of study endpoint.
2. The muscle strength score of the 3 groups that received active treatment initially are not comparable at Week 12. Therefore, comparing the change in muscle strength score from Week 12 to Week 52 is not meaningful except for patients randomized initially to placebo and re-randomized at Week 12. However, based on the protocol, patients randomized initially to placebo will be "evaluated in a descriptive fashion between 12 and 52 weeks of treatment after randomization to active medication".
3. The endpoint of change in average muscle strength score from baseline to Week 52 makes more sense based on the study design. Patients included in this analysis were randomized at baseline and received the same double blinded treatment as assigned for the whole 52 weeks.

3.2.1.2 Statistical Methodologies

The efficacy analysis set is based on the Intent-to-Treat (ITT) Population, consisting of all patients randomized into the study.

The primary analysis method specified in the protocol is an analysis of covariance model (ANCOVA). The main effects included baseline muscle strength score, site and treatments. The statistical analysis plan changed the primary analysis from ANCOVA to a mixed-effect model repeated measures (MMRM). The applicant's reason for the change was that the technology to perform MMRM was not yet available at the time the study was conducted, but is the most appropriate analysis technique for data that were collected repeatedly over time. The MMRM

model included treatment group, visit, treatment by visit, stratum (ambulatory/nonambulatory), and site as fixed effects. The baseline muscle strength score was included as a continuous covariate.

The 3 contrasts of each active treatment vs. placebo were evaluated as primary outcome. The overall significance level was to be adjusted by the Dunnett technique.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 196 patients were randomized to the 4 treatment groups, with 46 to 51 patients in each group. Data regarding discontinuation or completion of the study for each patient could not be obtained due to missing source documents. In an evaluation based on study visit dates, an estimated 189 patients completed study Segment 1 and 156 patients completed the study Segment 2. All patients were male, predominantly Caucasian (94.4%). The mean age was 8.8 years. Overall, disease characteristics were similar at baseline among treatment groups (Table 2).

Table 2: Study NM-001: Demographic and Baseline Disease Characteristics

Variable	Deflazacort 0.9 mg/kg/day N = 51	Deflazacort 1.2 mg/kg/day N = 49	Prednisone 0.75 mg/kg/day N = 46	Placebo N = 50	Total N = 196
Age (years)					
N	50	49	46	50	195
Mean (SD)	8.8 (2.53)	8.8 (3.04)	8.8 (2.94)	8.5 (3.09)	8.8 (2.89)
Race, n (%)					
Caucasian	46 (90.2%)	45 (91.8%)	45 (97.8%)	49 (98.0%)	185 (94.4%)
Asian	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Other	5 (9.8%)	3 (6.1%)	1 (2.2%)	1 (2.0%)	10 (5.1%)
Average Muscle Strength					
N	51	49	46	50	196
Mean (SD)	6.11 (1.481)	6.06 (1.400)	6.23 (1.619)	6.29 (1.421)	6.17 (1.471)
Functional Grading – Leg-Function Grading					
N	51	49	46	50	196
Mean (SD)	4.2 (3.37)	3.8 (3.09)	3.5 (3.28)	3.5 (3.10)	3.8 (3.20)
Functional Grading – Arm-Function Grading					
N	51	49	46	50	196
Mean (SD)	1.9 (1.26)	1.9 (1.39)	1.7 (1.31)	1.9 (1.37)	1.9 (1.33)
Physician Global Assessment					
n	51	49	46	50	196
Mean (SD)	10.99 (4.294)	10.17 (4.747)	9.61 (4.668)	10.22 (4.589)	10.26 (4.565)

Source: Table 7 & 8 of the study report.

3.2.1.4 Results and Conclusions

Analyses of the Primary Endpoint

For the primary analysis of the change from Baseline at Week 12 in muscle strength score by MMRM, there are two differences between the applicant's analysis and the reviewer's analysis.

1. In the applicant's analysis, data up to Week 52 were utilized by the MMRM to estimate the between-treatment difference at Week 12. This reviewer didn't include data after week 12 in the MMRM analysis as the primary objective of the study is to compare active drug to placebo at Week 12, and placebo treatment is only for the first 12 weeks.
2. Although not specified in the SAP, the applicant used compound symmetry covariance structure for all MMRM models in the submission for consistency as the model did not converge using unstructured covariance for some efficacy variables. This reviewer used unstructured covariance matrix for the primary endpoint and the model did converge.

Despite the two differences, the applicant's analysis (Table 3) and the reviewer's analysis (Table 4) showed similar results. Both analyses showed a statistically significant difference between active treatment and placebo for each of the 3 active treatment groups. An increase in average muscle strength was observed at Week 12 in each of the active treatment groups, compared to a decrease in average muscle strength in the placebo group. Differences from placebo in change from baseline in the muscle strength score are 0.25, 0.35 and 0.37 for the deflazacort 0.9 mg/kg/day group, the deflazacort 1.2 mg/kg/day group and the prednisone group, respectively.

Table 3: Study NM-001: Sponsor's Analysis of Change from Baseline at Week 12 in Average Muscle Strength Score Comparing Active Drug to Placebo

Treatment	N	n	Change from Baseline	Between-treatment Difference in Change from Baseline		
			LS Mean (95% CI)	Active - Placebo	95% CI	P-value
Deflazacort 0.9 mg/kg/day	51	48	0.15 (0.01, 0.28)	0.25	(0.04, 0.46)	0.0173
Deflazacort 1.2 mg/kg/day	49	46	0.26 (0.12, 0.40)	0.36	(0.14, 0.57)	0.0003
Prednisone 0.75 mg/kg/day	46	45	0.27 (0.13, 0.41)	0.37	(0.15, 0.59)	0.0002
Placebo	50	50	-0.10 (-0.23, 0.03)	-	-	-

Analysis results are from a mixed model of repeated measurements with compound symmetry covariance matrix.
P-values and confidence intervals are based on the Dunnett technique.
N: number of randomized subjects.
n: number of subjects with assessment at Week 12.
Source: Table 9 in the study report.

Table 4: Study NM-001: Reviewer's Analysis of the Primary Endpoint by MMRM

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean (95% CI)	Active - Placebo	95% CI	P-value
Deflazacort 0.9 mg/kg/day	49	0.18 (0.06, 0.30)	0.25	(0.06, 0.44)	0.0047
Deflazacort 1.2 mg/kg/day	48	0.29 (0.16, 0.41)	0.36	(0.17, 0.55)	<0.0001
Prednisone 0.75 mg/kg/day	46	0.30 (0.17, 0.42)	0.37	(0.18, 0.56)	<0.0001
Placebo	50	-0.07 (-0.19, 0.05)	-	-	-

Analysis results are from a mixed model of repeated measurements with unstructured covariance matrix.
P-values and confidence intervals are based on the Dunnett technique.
N: number of subjects with at least one post-baseline assessment within 12 weeks.
Source: FDA reviewer.

Additionally, this reviewer performed the ANCOVA as it is the pre-specified primary analysis in the protocol and it is a valid analysis for the collected data. Although the ITT Population includes all patients randomized into the study, the handling of dropouts or missing data is not specified in the protocol. To include subjects with missing Week 12 assessment in the analysis, the last observation carried forward approach (LOCF) was used in the reviewer's analysis. As the amount of missing data at Week 12 is very limited (4%), the impact of missing data on the analysis result is minimal. The results of ANCOVA (Table 5) are similar to the results of MMRM.

Table 5: Study NM-001: Reviewer's Analysis of the Primary Endpoint by ANCOVA

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean	Active - Placebo	95% CI	P-value
Deflazacort 0.9 mg/kg/day	49	0.20	0.25	(0.06, 0.43)	0.0059
Deflazacort 1.2 mg/kg/day	48	0.31	0.35	(0.16, 0.54)	<0.0001
Prednisone 0.75 mg/kg/day	46	0.34	0.38	(0.19, 0.57)	<0.0001
Placebo	50	-0.05	-	-	-

Analysis results are from an analysis of covariance with last observation carried forward.
P-values and confidence intervals are based on the Dunnett technique.
N: number of subjects with at least one post-baseline assessment within 12 weeks.
Source: FDA reviewer.

Analyses of the Key Secondary Endpoint
The reviewer's analysis of the change from Baseline to Week 52 in muscle strength score by MMRM showed no significant difference between the deflazacort groups and the prednisone group (Table 6).

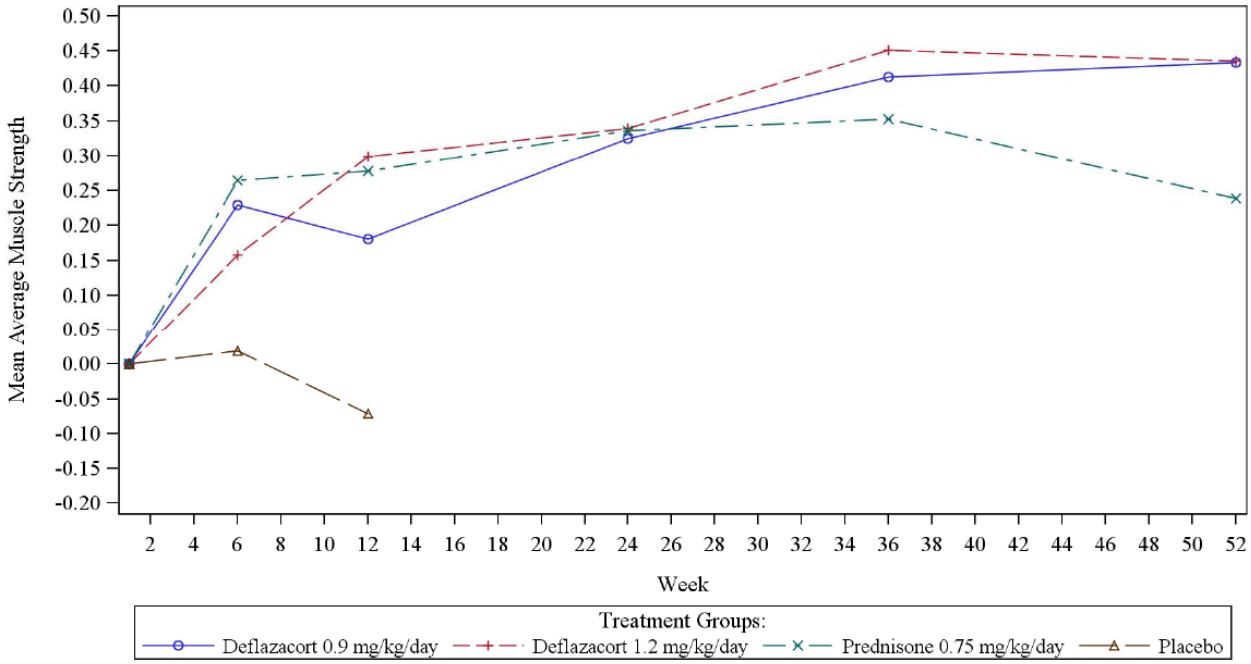
Table 6: Study NM-001: Reviewer's Analysis of Change from Baseline to Week 52 in Average Muscle Strength Score Comparing Deflazacort to Prednisone

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Deflazacort 0.9 mg/kg/day	49	0.42 (0.25, 0.59)	0.16	(-0.10, 0.43)	0.2830
Deflazacort 1.2 mg/kg/day	48	0.42 (0.24, 0.59)	0.16	(-0.11, 0.43)	0.3070
Prednisone 0.75 mg/kg/day	46	0.26 (0.08, 0.43)	-	-	-

Analysis results are from a mixed model of repeated measurements with unstructured covariance matrix.
P-values and confidence intervals are based on the Dunnett technique.
N: number of subjects with at least one post-baseline assessment within 52 weeks.
Source: FDA reviewer.

The applicant considered "average muscle strength score from Week 12 to Week 52" to be the key secondary endpoint and claimed a statistically significant difference between the deflazacort 0.9 mg/kg/day group and the prednisone group. However, in the option of this reviewer, the analysis result for the change from Week 12 to Week 52 is not interpretable. The larger increase in muscle strength score from Week 12 to Week 52 in the deflazacort 0.9 mg/kg/day group is mostly due to a lower score at Week 12 in this group, as shown in Figure 2. Because the groups are not comparable at Week 12, the comparisons of the treatment effect from Week 12 to Week 52 are not meaningful.

Figure 2. Study NM-001: Change from Baseline in Average Muscle Strength Score by Visit



Source: Figure 14.2.1 of the study report.

3.2.2 Study NM-002

3.2.2.1 Study Design and Endpoints

The supporting pivotal study NM-002 was conducted at 5 centers in Italy between 1988 and 1991. The SAP was written by Marathon and finalized on March 5, 2015. The protocol submitted by the applicant does not contain information on the statistical analysis methods.

Study Design

The study was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of deflazacort in the improvement of muscle strength in ambulatory male patients with DMD aged 5 to 11 years old at study entry. The study planned for 38 patients. Patients received deflazacort (2 mg/kg once every 2 days) or placebo in a 2:1 ratio. Patients were to remain in the study for a period of 2 years or until loss of ambulation, whichever occurred first. Data collection continued for some patients for several more years. Additionally, patients continued to be treated beyond the initially planned 2 years.

Efficacy Endpoints

The primary efficacy endpoint was change in muscle strength from baseline to 2 years or loss of ambulation, whichever occurred first. The muscle strength was assessed using the MRC Scale on four muscles using a 0 to 5 scale. The MRC index was expressed as a percentage of "normal strength", calculated as: sum of 4 strength measurements/number of muscles tested*5*100%.

Key secondary efficacy endpoints were not pre-specified for this study.

3.2.2.2 Statistical Methodologies

The primary endpoint was to be analyzed using MMRM with terms for treatment, time point and their interaction, and with baseline score, age, and baseline Gower score as continuous covariates. An unstructured covariance matrix was to be used.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall, the study enrolled 31 patients into the 2 treatment groups. Of them, 2 randomized patients were excluded; one patient did not receive study medication, and one patient whose CRFs could not be located. Consequently, the evaluable patient population comprises 29 randomized patients for whom data are available, consisting of 18 patients treated with deflazacort and 11 patients treated with placebo. Of these, 14 patients of the deflazacort group and 3 patients of the placebo group completed the study treatment period for at least 2 years following the first dose.

Overall, the 2 treatment groups were comparable with regard to demographic and baseline characteristics (Table 7). The mean age was 8 years. Details of race/ethnic origin were not collected.

Table 7: Study NM-002: Demographic and Baseline Disease Characteristics

Variable	**Deflazacort N = 18**	**Placebo N = 11**	**Total N = 29**
Age (months)			
Mean (SD)	96.3 (14.36)	96.0 (16.03)	96.2 (14.73)
Min, Max	72, 120	68, 119	68, 120
Average muscle strength score			
Mean (SD)	4.118 (0.5696)	4.136 (0.6672)	4.125 (0.5967)
Min, Max	3.00, 5.00	3.00, 5.00	3.00, 5.00

Source: Table 4 of the study report.

3.2.2.4 Results and Conclusions

The sponsor's primary analysis by MMRM showed that the difference between the two groups in change in muscle strength at Year 2 (primary time point) was not statistically significant (p=0.2107, Table 8). The differences between the 2 treatment groups at Month 6 and Year 1 are nominally significant. Little change in muscle strength was seen in the deflazacort group at Month 6 and Year 1 (LSM change from Baseline: 0.57 and -0.18 respectively), compared with a decrease in average muscle strength in the placebo group (LSM change from Baseline: -6.40 and -8.71 respectively).

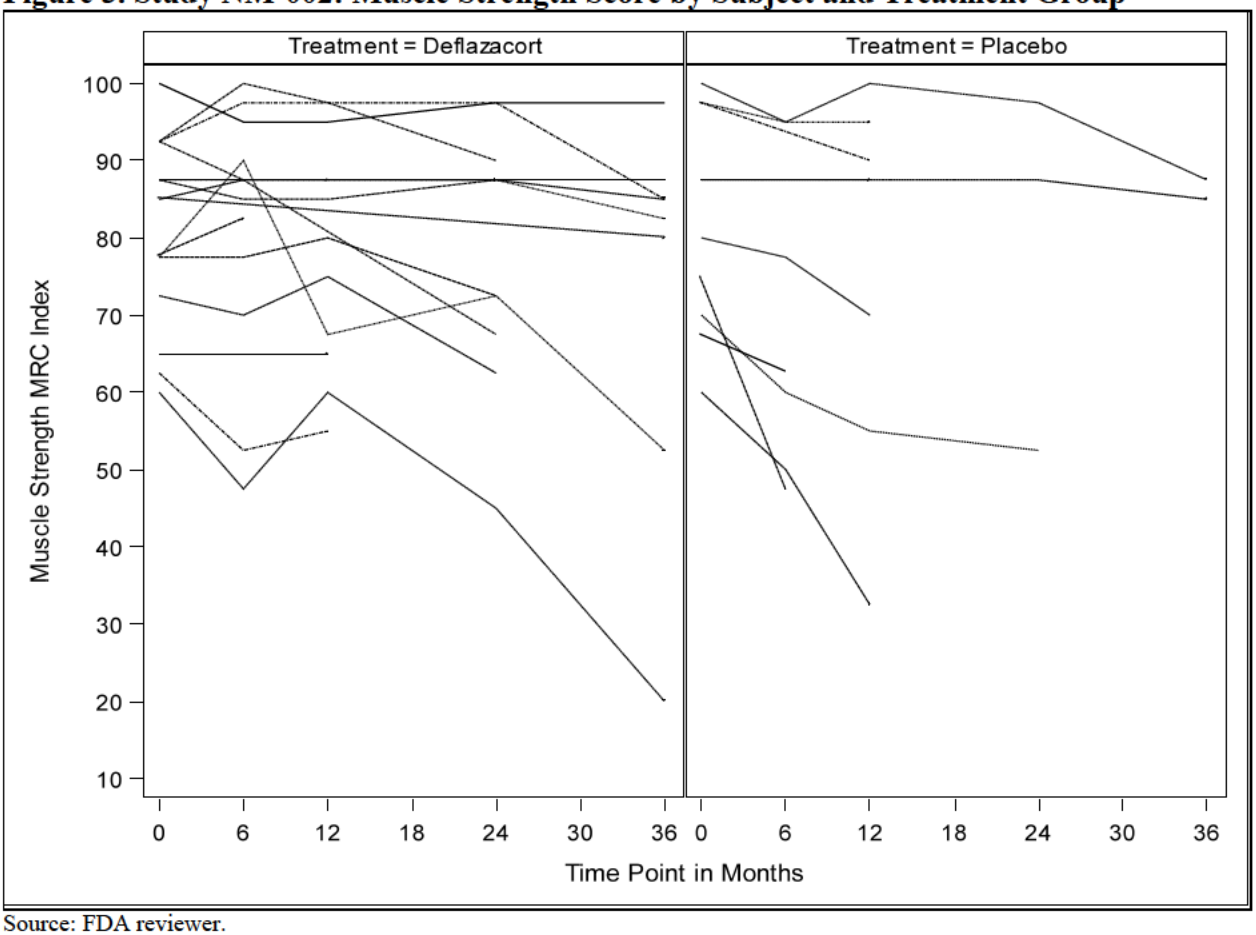
Table 8: Study NM-002: Analysis of Change from Baseline in Muscle Strength by MMRM

				Change from Baseline[1]	Between-treatment Difference in Change from Baseline[1]		
Visit	**Treatment**	**N**	**n**	**LS Mean (95% CI)**	**Deflazacort - Placebo**	**95% CI**	**P-value**
Month 6	Deflazacort	18	16	0.57 (-2.98, 4.12)	6.97	(1.24, 12.69)	0.0192
	Placebo	11	10	-6.40 (-10.84, -1.96)			
Year 1	Deflazacort	18	14	-0.18 (-3.73, 3.38)	8.53	(2.75, 14.32)	0.0056
	Placebo	11	9	-8.71 (-13.18, -4.25)			
Year 2	Deflazacort	18	12	-3.91 (-7.89, 0.08)	5.20	(-3.16, 13.56)	0.2107
	Placebo	11	3	-9.11 (-16.40, -1.82)			
Year 3	Deflazacort	18	8	-18.30 (-29.09, -7.51)	0.21	(-24.49, 24.91)	0.9861
	Placebo	11	2	-18.51 (-40.69, 3.67)			

N = total number of patients in each treatment group, n = number of patients available at the current visit
Source: Table 6 of the study report.

In Study NM-002, patients were to remain in the study for a period of 2 years or until loss of ambulation. There were 1 subject in the Deflazacort group and 3 subjects in the placebo group lost ambulation prior to Year 2. Additionally, there were many subjects dropped out/had missing data prior to Year 2. In the placebo group, only 3 out of 11 subjects had measurement on muscle strength at Year 2, and the 3 subjects had relatively stable muscle strength compared to those who dropped out/had missing data (Figure 3). The missing at random (MAR) assumption of MMRM analysis is unlikely to hold and the analysis result for Year 2 and beyond is difficult to interpret.

Figure 3. Study NM-002: Muscle Strength Score by Subject and Treatment Group



Source: FDA reviewer.

The definition of the primary efficacy endpoint (change in muscle strength from baseline to 2 years or loss of ambulation, whichever occurred first) indicating the use of the last available observations for the analysis. Based on analysis of covariance (ANCOVA) using the last available observation, deflazacort demonstrated less decline in muscle strength compared to placebo at Year 2 (LSM difference of 7.65, p = .0183, Table 9). As there were more subjects in the placebo group who lost ambulation or dropped out and had missing data, and the muscle strength could continue to decrease afterwards, the analysis with missing values accounted for by using last observation may yield a conservative estimate of the treatment effect. However, given the high percentage of missing data, any analysis of the treatment effect in muscle strength at Year 2 and beyond may not be conclusive.

Table 9: Study NM-002: Analysis of Change from Baseline in Muscle Strength at Year 2 by ANCOVA with Last Observation

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean (95% CI)	Deflazacort - Placebo	95% CI	P-value
Deflazacort	16	-2.81 (-6.69, 1.08)	0.16	(1.430, 13.877)	0.0183
Placebo	11	-10.46 (-15.18,-5.74)	-	-	-

Source: FDA reviewer.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Subgroup analysis is not applicable for gender (only males were included) or race (not collected in Study NM-002 and > 94% Caucasian in study MP-104-NM-001). Analysis of age subgroups for Study NM-002 is not conducted due to the small sample size. For Study NM-001, both age subgroups (<=median age, >median age) showed similar treatment effect in change from baseline at Week 12 in muscle strength score (Table 10).

Table 10: Study NM-001: Analysis of Change from Baseline at Week 12 in Average Muscle Strength Score by Demographic Subgroups

	Deflazacort 0.9 mg/kg/day	Deflazacort 1.2 mg/kg/day	Prednisone 0.75 mg/kg/day	Placebo
Baseline Age < 9				
n	21	24	25	30
Active - Placebo	0.24	0.25	0.39	-
95% CI	(-0.001, 0.474)	(0.022, 0.485)	(0.163, 0.619)	-
Baseline Age >= 9				
n	28	24	21	20
Active - Placebo	0.31	0.46	0.34	-
95% CI	(0.095, 0.518)	(0.236, 0.677)	(0.114, 0.566)	-

Source: FDA reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Both studies were conducted more than 20 years ago. The SAPs for the available data were drafted by the applicant in 2015. The analyses stated in SAP for Study NM-001deviated from those pre-specified in the original protocol. The data were not of high quality due to missing source document and lack of data management. Some variables (including subject disposition) were not available for all subjects and there were apparent data errors.

In the pivotal Study NM-001, the key secondary endpoint as specified in the protocol is not clear. This reviewer has a different position than the sponsor as to which should be the key secondary endpoint.

In the supportive Study NM-002, there was a high percentage of missing data at Year 2, leaving the analysis of the primary endpoint inconclusive.

5.2 Collective Evidence

The primary efficacy analysis from the pivotal study NM-001 demonstrated a statistically significant difference in average change in muscle strength score from Baseline to Week 12 in favor of the two deflazacort groups (0.9 mg/kg/day: $p = 0.0173$; 1.2 mg/kg/day: $p = 0.0003$) and the prednisone group ($p = 0.0002$) compared to placebo. The treatment effect is consistent between the age subgroups.

Supportive trial NM-002 investigated long-term treatment effect of deflazacort compared to placebo. The analysis result of the average change in muscle strength score at Year 2 (the primary time point) is not statistically significant, although it showed numerical trend favoring deflazacort. The analysis of Year 2 data was inconclusive because of the high percentage of missing data. The amount of missing data at Year 1 is limited, and the treatment effects in muscle strength score at Month 6 and Year 1 are nominally significant.

5.3 Conclusions and Recommendations

The data overall provide statistical evidence to support the efficacy of deflazacort in improving muscle strength in DMD subjects compared to placebo at 12 weeks.

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/s/

XIANG LING
11/08/2016

KUN JIN
11/09/2016
I concur with the review.

HSIEN MING J HUNG
11/09/2016