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APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 8, 2017
From	Nick Kozauer, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208684/208685
Applicant	Marathon Pharmaceuticals, LLC
Date of Submission	June 9, 2016
PDUFA Goal Date	February 9, 2017
Proprietary Name / Non-Proprietary Name	Emflaza (deflazacort)
Dosage Form(s)	Oral tablets (NDA 208684);Oral suspension (NDA 208685)
Dosage Strength	0.9 mg/kg/day
Applicant Proposed Indication(s)/Population(s)	Duchenne Muscular Dystrophy; Ages 5 (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Duchenne Muscular Dystrophy; Ages 5 and above

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Duchenne muscular dystrophy (DMD) is a rare genetic disorder that results from the inability to produce the dystrophin protein, which is produced by the dystrophin gene located on the X-chromosome. The dystrophin protein is located in muscle cells and plays a vital role in linking the muscle fiber to the surrounding extracellular matrix. The loss of dystrophin in DMD results in progressive muscle loss manifesting in progressively increasing weakness and fatigue. Patients universally lose the ability to ambulate (generally in their early teenage years) and death occurs most frequently as a result of cardiac and/or respiratory muscle failure (generally in their 3rd decade). The disease affects approximately 1 in 3600-6000 male births (females can be affected in extremely rare circumstances) and has a prevalence of approximately 1:7,250 males between 5-24 years of age.

Deflazacort (Emflaza) is a corticosteroid medication. Deflazacort itself is an inactive, ester pro-drug that is rapidly metabolized to the active metabolite 21-desacetyldeflazacort (21-desDFZ). Corticosteroids are used off-label as the standard of care for DMD in the United States (US). Deflazacort is not approved for any indication in the US, but is approved for a wide variety of uses in a number of countries worldwide. Deflazacort is not approved for the treatment of DMD in any country, but is often used for that purpose in clinical practice. Corticosteroids are known to have well-described immunosuppressive and anti-inflammatory effects, however, the exact mechanism of action that deflazacort has in the treatment of DMD is unknown.

There are no FDA-approved treatments for all patients with DMD. In September 2016, eteplirsen (Exondys 51) received an accelerated approval for the treatment of DMD patients with mutations that are amenable to exon 51 skipping therapies. This approval was based on the demonstration of increases in the dystrophin protein; the clinical benefit of these changes has not been established.

This application contains data from two clinical trials conducted in the 1990s that investigated the use of deflazacort in the treatment of DMD. Note that the applicant was able to successfully bridge the to-be-marketed formulation of deflazacort (Emflaza) to the formulations used in the clinical trials supporting an approval action. Study NM-001 was conducted in 196 subjects ages 5-15 years old at Screening and was able to establish a somewhat small but statistically significant effect of treatment on a 0-10 point clinical assessment of average muscle strength. Additional clinical endpoints in the trial, although they were not statistically controlled for multiple comparisons, were also generally supportive of the results on the primary endpoint. Study NM-002 was conducted in 29 patients with DMD who were 5-11 years old at Screening. The trial was not able to demonstrate a statistically significant effect of treatment on the primary endpoint of a 0-5 point clinical assessment of average muscle strength at 2 years. However, this finding is likely a function of the trial's design which required the withdrawal of subjects who lost ambulation resulting in only 3 placebo subjects remaining at that point. Additional analyses conducted at 6 months and 1 year, along with analyses of the effect of treatment on the ability to maintain ambulation longer, supported the efficacy of deflazacort for the treatment of DMD.

The clinical efficacy trials included in the application support the efficacy of deflazacort for the treatment of patients with DMD who are 5 years of age and older. However, the lack of any definitive efficacy information in patients below age 5, combined with the lack of safety information in this younger population, should limit the indication to patients who are above age 5 (b) (4)

Dr. Paine's clinical review details the adverse event profile of deflazacort which is consistent with the well described safety profile of corticosteroids based on extensive clinical experience in a wide range of indications. In addition to the known common adverse events with corticosteroids that are outlined in Dr. Paine's review (e.g., Cushingoid syndrome, erythema, hirsutism, weight gain, etc.), Emflaza should also be labeled for the known serious risks of corticosteroids that have resulted in class labeling (e.g., immunosuppression, psychiatric symptoms, etc.). Dr. Paine's review has also established a risk of toxic epidermal necrolysis (TEN) with deflazacort based on the published literature, which should also be included in the WARNINGS AND PRECAUTIONS section of the Prescribing Information (PI) for Emflaza. The serious and fatal nature of DMD supports that fact that despite the known risks of treatment, an approval action can be taken for Emflaza for the treatment of DMD with appropriate safety labeling so the patients/healthcare providers/caregivers can make informed treatment decisions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne muscular dystrophy (DMD) is a rare progressive X-linked neuromuscular disorder that results from mutations in the dystrophin gene and affects approximately 1 in 3600-6000 male births, with a prevalence of approximately 1 in every 7,250 males ages 5-24 years. Patients experience progressive muscle weakness eventually leading to a loss of ambulation and death, most typically resulting from the loss of respiratory and/or cardiac muscle function.	DMD is a universally progressive disease that leads to serious disability. Death typically occurs in a patient's third decade.
Current Treatment Options	• There are no FDA-approved treatments for all patients with DMD. In September 2016, eteplirsen (Exondys 51) received an accelerated approval for the treatment of DMD patients with mutations that are amenable to exon 51 skipping therapies. This approval was based on the demonstration of increases in the dystrophin protein; the clinical benefit of these changes has not been established.	There are no FDA-approved treatments for all patients with DMD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The application included data from two randomized, double-blind trials conducted in the 1990s. • Study NM-001 was conducted in 196 subjects with DMD ages 5-15 years at Screening and compared 0.9mg/kg/day and 1.2 mg/kg/day doses of deflazacort to placebo for 12 weeks. Comparisons to 0.75 mg/kg/day of prednisone were also made at Weeks 12 and 52. Study NM-001 demonstrated an effect of deflazacort over placebo at Week 12 (the latest timepoint that allowed for a placebo comparison) on its primary endpoint, a mean measure of muscle strength (i.e., the 0-10 point modified Medical Research Council scale). Importantly, the scores on this measure continued to increase through 52 weeks of treatment in the deflazacort arms, which is inconsistent with the progressive nature of DMD. Despite not being statistically controlled for multiple comparisons, results on 3 of 4 timed-function tests from Study NM-001 demonstrated highly nominally significant effects of deflazacort as compared to placebo at Week 12. • Study NM-002 evaluated a 2 mg/kg dose of deflazacort given every other day in comparison to placebo for up to 3 years in 29 subjects with DMD ages 5-11 at Screening. The trial failed to demonstrate a statistically significant effect on its primary endpoint, a 0-5 point version of the MRC scale at Year 2. However, the trial, by design, withdrew subjects when they lost the ability to ambulate leaving only 3 placebo subjects remaining at Year 2, substantially impacting the interpretability of these results. Results of the comparison between treatment and placebo at Month 6 and Year 1 both reached nominal significance. Additionally, subjects on treatment had nominally significant longer times to loss of ambulation (63 months versus 32 months) with 5 of 9 dropouts in placebo by Year 3 doing so because of a loss of ambulation as compared to only 1 of 10 dropouts at Year 3 in placebo. • Although not formally considered during the review of this application, corticosteroids are widely accepted as the standard of	This application has established that deflazacort is effective for the treatment of patients with DMD. An approval action for DMD patients ages 5 and older is recommended. Although it is plausible that deflazacort is also effective in patients less than 5 years of age, the lack of definitive evidence of efficacy combined with an absence of safety information (see below) in this population do not support an indication in these younger patients (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	care for the treatment of DMD worldwide.	
Risk	• Deflazacort carries the expected risks that are well-known to be associated with corticosteroid administration. • The most commonly observed (≥ 10%) adverse events associated with the use of deflazacort in clinical studies were Cushingoid (59%), erythema (35%), hirsutism (34%), weight increased (27%), headache (25%), nasopharyngitis (22%), central obesity (22%), pollakiuria (13%), increased appetite (12%), abdominal pain (11%), constipation (11%), upper respiratory tract infection (11%), and influenza (11%). • A range of psychiatric adverse events were reported at a greater rate in the deflazacort groups compared to placebo: abnormal behavior (6.8%), irritability (5.1%), aggression (4%), psychomotor hyperactivity (4%), affect lability (2.3%), and mania (0.6%). • Additionally, several cases consistent with toxic epidermal necrolysis (TEN) that were associated with deflazacort use in non-DMD patients were identified in the published literature.	The risks of deflazacort treatment are consistent with the well-established safety profile of corticosteroid therapy. The serious nature of DMD justifies an approval action in the setting of the established efficacy of deflazacort. However, deflazacort should not be indicated for DMD patient less than 5 years of age given the lack of safety information in these patients, the known potential for serious toxicities in older patients, and the lack of established efficacy in patients less than age 5 (see above).
Risk Management	• Strong product labeling for the numerous known safety risks with corticosteroids, including deflazacort, is necessary.	The WARNINGS AND PRECAUTIONS section of the product label will comprehensively reflect recently revised Agency class labeling for corticosteroids. An additional WARNINGS AND PRECAUTIONS item will also describe the risk of TEN that was identified.

2. Background

This memorandum will jointly discuss applications for two formulations of deflazacort (oral tablets and oral solution) for the treatment of Duchenne Muscular Dystrophy (DMD). For simplicity, these submissions will be discussed as a single application. Deflazacort is considered a new molecular entity (NME) and has not been approved in the United States (US) for any indication and has not previously been the subject of any marketing application. Various formulations of deflazacort are approved in other regions of the world for the treatment of a number of non-DMD indications. The only FDA-approved treatment for DMD is eteplirsen (Exondys 51) which received a biomarker-based accelerated approval in September 2016 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amendable to exon 51 skipping (clinical efficacy in these patients has not been established).

DMD is a rare progressive X-linked neuromuscular disorder that results from mutations in the dystrophin gene and affects approximately 1 in 3600-6000 male births, with a prevalence of approximately 1 in every 7,250 males ages 5-24 years old. The dystrophin protein is involved in muscle contraction and is responsible for connecting the cytoskeleton of muscle fibers to the surrounding extracellular matrix. Over time, patients continue to experience progressive and profound muscle weakness and have an average life expectancy of 26 years, generally dying from respiratory and/or cardiac muscle involvement.

Deflazacort is an inactive pro-drug that is rapidly metabolized to the activity moiety, 21-desacetyldeflazacort (21-desDFZ). Deflazacort is a glucocorticoid, a member of the corticosteroid class of medications, that is purported to have anti-inflammatory and immunosuppressive properties.

This application contains data from two randomized, double-blind, placebo- and active-controlled (in 1 trial) clinical trials that were conducted in the early 1990s that are intended to provide the support for the efficacy of deflazacort in the treatment of DMD.

The regulatory history for deflazacort in DMD is detailed in Dr. Rainer Paine's clinical review and the reader is referred there for additional information.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann (Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application). The OPQ review team concludes that this application is approvable, from their perspective. Dr. Heimann's review notes the application, as amended, provides adequate information to ensure that the product can be consistently manufactured in a manner that is suitable for use by the intended patient population.

The OPQ review notes that all facilities that will be involved in the commercial manufacture and testing of the drug products (i.e., the tablets and oral suspension) are acceptable.

Dr. Heimann notes that the label administration instructions for the oral suspension recommend mixing the measured dose with 3 to 4 ounces of (b) (4) juice, or whole milk. However, based on degradation observed during in-use studies, OPQ further recommends that the dose should then be administered immediately.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. David Hawver, with Dr. Lois Freed performing a secondary review. Dr. Hawver concludes that the nonclinical data that have been provided with the application do not adequately support the approval of deflazacort for the treatment of DMD. The basis for this finding is the fact that insufficient information has been provided to determine if major circulating human metabolites M-V or 6β-OH-21-desDFZ have been adequately assessed for genotoxicity and carcinogenicity or if M-V has been adequately assessed for chronic toxicity. Dr. Hawver comments that if an approval action is taken, these deficiencies should be assessed though postmarketing requirements (PMRs).

The following are among the key additional conclusions from Dr. Hawver's review:

- Dr. Hawver discusses a variety of both in vitro and in vivo data that support the possible mechanisms of effect of deflazacort in DMD (e.g., improved muscle repair, immunosuppression, and anti-inflammatory effects).

- Pivotal toxicity studies were conducted in monkeys (39-week study), adult rats (26-week study), and juvenile rats (8-week study). The primary effects in all three studies were immunosuppression (lymphocytic depletion and/or hypocellularity of lymphoid organs, reduced circulating lymphocytes, and/or impaired T-cell dependent antibody response) and atrophy of adrenal cortex and other organs. Additional effects observed in juvenile rats included adverse effects on neurological, functional, and neurobehavioral parameters and bone growth.

- A published 2-year carcinogenicity study of deflazacort in rat demonstrated a combined incidence osteoma and osteosarcoma of 14% in males at the maximum tolerated dose compared to 0% in controls; a similar study in mice was reported to be negative, but no description of the study was provided.

- Mean 21-desDFZ plasma exposures (AUC) at the no-observed adverse effect levels (NOAELs) for male monkey, adult rat, and juvenile rat were 4, 0.15, and <0.27 times, respectively, that in adolescent DMD patients administered the recommended clinical dose of 0.9 mg/kg/day deflazacort. There is no safety margin for the adverse effects observed in adult or juvenile male rats.

If an approval action is taken, Dr. Hawver plan to recommend that a PMR is imposed (in addition to the metabolite studies, discussed above) to assess the feasibility of conducting an oral carcinogenicity study in mouse, with the requirement to conduct such a subsequent carcinogenicity study, if warranted. Dr. Hawver has concluded that the applicant has justified a waiver request

related to conducting a 2-year carcinogenicity study in rat as it would not be likely to provide new meaningful information beyond a published study that was submitted with the application.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Bilal AbuAsal (the primary reviewer), Dr. Atul Bhattaram, Dr. Ping Zhao, Dr. Kevin Krudys, and Dr. Sreedharan Sabarinath (the clinical pharmacology team lead).

The following table, reproduced from information provided in the OCP review, summarizes the pharmacokinetic properties of deflazacort:

Mechanism of Action	Deflazacort is a pro-drug that is metabolized rapidly in the plasma by esterases to the active moiety 21-desacetyl deflazacort (21-desDFZ).
Absorption	The median T_{max} for tablets taken without food in about 1 hour, co-administration with a high-fat meal did not affect absorption, administration in applesauce did not affect bioavailability, and the tablet and suspension formulations are bioequivalent.
Distribution	The plasma binding of 21-desDFZ is about 40%.
Metabolism	Plasma esterases are responsible for the conversion of deflazacort to its active metabolite, 21-desDFZ. 21-desDFZ is then further metabolized by CYP3A4 to inactive moieties.
Elimination	The mean terminal half-life of 21-desDFZ ranged from 2-3 hours.

Bridging Between the Clinical Trial Formulation and the To-Be-Marketed Formulation

The clinical trials intended to support the approval of deflazacort for the treatment of DMD were conducted in the early 1990's, and a direct bridging to the to-be-marketed formulation (EMFLAZA) was not feasible. In addition, no pharmacokinetic (PK) information was collected in those trials. Therefore, the OCP review discusses a detailed consideration of the totality of the evidence provided in this application that would support the establishment of an indirect bridge between EMFLAZA and the formulation used in the clinical efficacy trials. Considerations included the fact that clinical pharmacology studies with different formulations of deflazacort (e.g., oral suspension, oral tablet, etc.) have demonstrated little sensitivity to formulation changes, there is no apparent food effect, there is an estimated 95% absorption from the gastrointestinal tract, and that there did not appear to be any relationship between dose and efficacy in the clinical trials. Based on these findings, the OCP review concludes that the intrinsic properties of deflazacort are sufficient to ensure absorption regardless of pH and formulation changes, and that EMFLAZA is unlikely to have lower bioavailability than the clinical formulation used in the efficacy trials submitted with this application.

The OCP review also finds that bioavailibity has been established between the commercial oral suspension of deflazacort (36mg/1.68mL) (i.e., Calcort, which is approved in other regions of the world for non-DMD indications) in apple juice versus EMFLAZA (36mg).

Dosing Recommendations

The OCP review agrees with the applicant's original proposal of a body weight-based doing regimen (i.e., 0.9 mg/kg/day). The review also discusses a revised proposal made by the applicant during the review cycle to recommend a flat dosing scheme based on three body weight categories. This proposal also included a differential dosing scheme based on the ambulatory status of a patient. However, the OCP review concludes that this flat dosing scheme could potentially expose some

patients to doses that are 14-40% lower based on the weight cut-off, than the 0.9mg/kg dose, and continues to recommend the original weight-based dosing approach. The OCP review also concludes that the currently available data does not support the applicant's rationale for administering higher doses in non-ambulatory patients.

The OCP review recommends a 3-fold reduction in dose when concomitant use of a moderate or strong CYP3A4 inhibitor is required and the avoidance of use with moderate or strong CYP3A4 inducers. The OCP review also concluded that no dosage adjustments need to be made for patients with mild to moderate hepatic impairment, or renal impairment. No dosing recommendations for patients with severe hepatic impairment can be made because of the limited clinical experience in this population. The OCP review further concludes that no dosing adjustments are required based on age, sex, or race.

Metabolites
The OCP review team agrees with the nonclinical review that the metabolite referred to as M-V has not been adequately characterized, and is therefore recommending a PMR to characterize the deflazacort metabolites circulating in human plasma. The OCP review also recommends a PMR to characterize the potential for CYP and transporter-mediated interactions due to inhibition or induction of these enzymes and transporters in vitro by the 6β-OH-metabolite (M-III).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

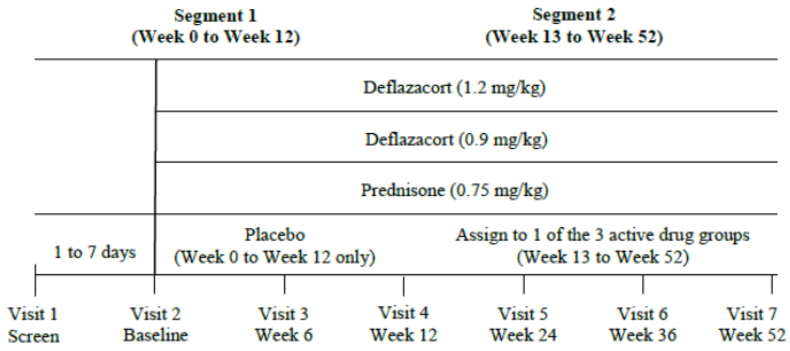
Dr. Rainer Paine was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead for this application.

Study MP-104-NM-001
Study MP-104-NM-001 (Study NM-001) was intended to be the primary trial supporting the efficacy of Emflaza for the treatment of DMD. The trial was a double-blind, randomized, placebo- and active-controlled study in patients with either DMD or Becker Muscular Dystrophy (BMD) [almost all patients were ultimately diagnosed with DMD]. Subjects were between 5-15 years old at Screening, with an onset of weakness before age 5 and increased serum creatinine kinase (CK) activity at least 10X the upper limit of normal (ULN) at some stage in their illness. Genetic confirmation of a mutation in the dystrophin gene and alterations in the amount and/or distribution of dystrophin in muscle were also required. Randomization was stratified by center and ambulation status (ambulatory vs. non-ambulatory).

The trial was conducted by (b) (4) The current applicant completed the data analysis and issued the clinical study report (CSR) after the original sponsor transferred the rights to Dr. Fenichel at Vanderbilt University.

The trial evaluated two doses of deflazacort and one dose of prednisone compared to placebo for 12 weeks in Segment 1, and two doses of deflazacort compared to one dose of prednisone for an

additional 40 weeks in Segment 2 (subjects receiving placebo in Segment 1 were randomized to one of the three active treatment arms in Segment 2 after Week 12). The following graphic, copied from the application, summarizes the design of Study NM-001:



196 subjects were enrolled, with 51 randomized to receive deflazacort 0.9 mg/kg/day, 49 randomized to receive deflazacort 1.2 mg/kg/day, 46 randomized to receive prednisone 0.75 mg/kg/day, and 50 initially randomized to receive placebo (for Segment 1).

The primary endpoint for the trial was the change from Baseline to Week 12 in muscle strength as assessed by the 11-point modified version of the Medical Research Council (MRC) muscle strength assessment. Dr. Paine's review provides additional detail regarding this scale, which takes the takes the average of the strength assessments of 34 muscles, which are rated on a 0-10 scale (with 10=normal strength and 0=no movement).

Dr. Ling's review comments that the original protocol specified an ANCOVA model for the primary endpoint analysis (i.e., change from Baseline in the mean MRC score at Week 12). However, the statistical analysis plan (SAP) drafted in January 2015 specified an MMRM analysis which the applicant attempted to justify based on the fact that such an analysis was not yet developed at the time the protocol was written and that it would be the most appropriate technique for data collected repeatedly over time. Dr. Ling finds this change acceptable but notes two main differences between the analysis of the primary endpoint that she conducted, as compared to the applicant's analysis, including:

- The fact that the MMRM used in the applicant's analysis utilized data from up to Week 52 to estimate the between-treatment difference at Week 12, which she did not feel was appropriate as the primary analysis was at Week 12, and placebo treatment was only for the first 12 weeks, and;

- The applicant used a 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. However, Dr. Ling used an unstructured covariance matrix for the primary endpoint and the model did converge.

Despite these differences, Dr. Ling indicates that the two approaches yielded similarly positive results, as depicted in the following tables copied from her review which display the results of the applicant's and her own analysis, 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.

As an additional analysis, Dr. Ling also completed an analysis of the primary endpoint based on the ANCOVA approach described in the original protocol. As the handling of drop-outs was not described, Dr. Ling used the last observation carried forward (LOCF) approach noting that the amount of missing data at Week 12 was very low (4%), so the impact on the analysis of how these data are handled is minimal. The following table, copied from Dr. Ling's review, summarizes the results of this analysis:

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.

Dr. Ling's review describes a lack of clarity in the protocol as to the planned key secondary endpoint, which was described in different sections of the protocol as either being the change in MRC score from Week 12 to Week 52 (i.e., Segment 2), or from Baseline to Week 52. However, Dr. Ling

contends that the analysis of the change from Baseline to Week 52 is most appropriate because of several reasons including the most common descriptions of the endpoint in the protocol, the lack of comparability of the initial 3 active-treatment arms at Week 12, and the fact that subjects continued on treatment for all 52 weeks making it a more logical analysis based on the trial design. The following table, copied from Dr. Lin's review, summarizes the results of the key secondary endpoint analysis based on the change from Baseline to Week 52:

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.

Dr. Ling goes on to note that the applicant's analysis of the key secondary endpoint, based on the change from Week 12 to Week 52 in mean MRC scores, reports a statistically significant difference between the Emflaza 0.9 mg/kg/day arm and the prednisone arm. However, Dr. Ling finds this result uninterpretable as 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.

Only the primary and key secondary endpoints were statistically controlled for multiple comparisons. Therefore, as Dr. Paine notes in his review, analyses of the additional secondary endpoints can only be considered as exploratory. The additional endpoints that were evaluated include the following:

- Pulmonary function testing
- Timed function testing
- Quantitative myometry
- Functional grading
- Physician global assessment

The detailed results of the analyses of these endpoints are outlined in Dr. Paine's review, including a description of the nature and operationalization of the specific measures. Below are the findings from these analyses, focusing on the comparison of the deflazacort arms to placebo at Week 12. As Dr. Paine notes, there were no clear advantages of deflazacort as compared to prednisone in the Baseline to Week 52 comparisons.

- Relatively small numerical trends towards benefit were observed on the change from Baseline on both forced vital capacity (FVC) and maximum voluntary ventilation (MVV) at Week 12, although none reached nominal statistical significance. Dr. Paine comments that the relatively intact nature of the pulmonary function in the subjects enrolled in the trial likely limits the ability to detect a treatment effect in this population.

- Nominally significant results were observed in the change from Baseline to Week 12 in the time to stand from supine (in seconds) for the comparison of both deflazacort groups to placebo (-1.83 in the deflazacort 0.9 mg/kg/day arm versus 2.11 in the placebo arm; p=0.0018) (-2.78 in the deflazacort 1.2 mg/kg/day arm versus 2.11 in the placebo arm; p=0.0002). There was no difference between either of the deflazacort arms and prednisone at Week 12.

- Nominally significant results were observed in the change from Baseline to Week 12 in the 4-stair climb (4SC) (in seconds) for the comparison of both deflazacort groups to placebo (-2.48 in the deflazacort 0.9 mg/kg/day arm versus 1.15 in the placebo arm; p<0.0001) (-2.99 in the deflazacort 1.2 mg/kg/day arm versus 1.15 in the placebo arm; p<0.0001). There was no difference between either of the deflazacort arms and prednisone at Week 12.

- Nominally significant results were observed in the change from Baseline to Week 12 in the time to run/walk 30 feet (in seconds) for the comparison of both deflazacort groups to placebo (-19.48 in the deflazacort 0.9 mg/kg/day arm versus 6.11 in the placebo arm; p<0.0001) (-2.84 in the deflazacort 1.2 mg/kg/day arm versus 6.11 in the placebo arm; p<0.0001). There was no difference between either of the deflazacort arms and prednisone at Week 12.

- The change from Baseline to Week 12 in quantitative myometry testing (QMT) which averaged results over three muscle groups (i.e., shoulder abduction, elbow flexion/extension, and knee flexion/extension) yielded a nominally significant result favoring the deflazacort 1.2 mg/kg/day arm as compared to placebo (+17.49% [sd=26.03] versus +5.83% [sd=30.58], respectively; p=0.0082). The +38.16% result in the deflazacort 0.9 mg/kg/day arm was not nominally significant (p=0.0599), potentially because of the significant variability in the results (sd=155.895).

- There were no clear numerically or statistical trends towards benefit in the analyses of mean functional leg grading scores (using a 10-point scale, ranging from grade 1, “walks and climbs stairs without assistance,” to grade 10, “is confined to bed.” In the functional arm grading assessment (using a 6-point scale, ranging from grade 1, “starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head,” to grade 6, “cannot raise hands to mouth and has no useful function of hands.” there was a nominally significant difference in the change from Baseline in the comparison of the deflazacort 1.2 mg/kg/day arm versus placebo (-0.10 versus 0.14, respectively; p=0.0156). There was a small numerical difference in the comparison of the deflazacort 0.9 mg/kg/day arm versus placebo that was not nominally significant (0.03 versus 0.14, respectively; p=0.50).

- Only a very small numerical advantage in the change from Baseline on a physician global assessment using a visual analog scale (0 = “no symptoms;” and 100 = “as bad as it could be”) were evident in the comparisons between the deflazacort arms (0.70 and 0.79 for the deflazacort 0.9 mg/kg/day and 1.2 mg/kg/day arms, respectively) and placebo (0.98) at Week 12, none of which came close to achieving nominal significance.

Study MP-104-NM-002

Study MP-104-NM-002 (Study NM-002) was intended to support the efficacy of deflazacort for the treatment of DMD that the applicant believes was established in Study NM-001. This supporting trial was conducted at 5 centers in Italy between 1988-1991. The SAP was written by the applicant and finalized in March 2015. The original protocol does not contain information on the statistical analysis methods.

The trial was a double-blind, randomized, placebo-controlled study in ambulatory DMD patients 5-11 years old at Screening. Subjects were required to have an onset of symptoms before age 5 and a DMD diagnosis confirmed by a neurological examination, electromyography, serum testing, and a muscle biopsy. Subjects were randomized in a 2:1 ration to receive either deflazacort (2 mg/kg every 2 days) or placebo. Subjects were to remain in the trial for 2 years or until they lost the ability to ambulate, whichever came first. Some subjects were however treated for beyond the planned initial 2 year period.

Dr. Ling notes that 31 subjects were enrolled, although 2 randomized patients were excluded from the final analysis; one because they did not receive study medication and one whose CRFs could not be located. Therefore, 29 subjects were included in the analysis, consisting of 18 in the deflazacort arm and 11 in the placebo. However, only 14 of the subjects in the deflazacort arm and 3 of the subjects in the placebo arm remained in the trial for at least 2 years.

The trial's primary endpoint was the change in muscle strength from Baseline to 2 years or the loss of ambulation, whichever occurred first. Dr. Paine's review describes the muscle strength endpoint as using a 0-5 point verbal rating scale that was converted to a "MRC index score." The grading scale, outlined in detail in Dr. Paine's review, is scored from 0 (no movement) to 5 (normal contraction against full resistance). Intermediate scores of 0.5 (e.g., 2.5) were also allowed. This score was then expressed as a percentage of normal strength for the sum of four strength measurements (i.e., right triceps, right deltoid, right quadriceps, and right iliopsoas). The primary endpoint was analyzed using an MMRM procedure, as described in further detail in Dr. Ling's review.

The following table, copied from Dr. Ling's review, presents the results of the primary endpoint analysis:

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.

As Dr. Ling notes, the results at the prespecified primary timepoint of 2 years were not statistically significant. However, the fact that only 3 placebo subjects were remaining at Year 2 greatly impacts the interpretability of this result. As the table indicates, the differences between the treatment arms at Month 6 and Year 1 were nominally significant. Dr. Ling also makes the important observation that the deflazacort arm did not appear to decline to a great extent at these points 0.57 and -0.18, respectively), relative to placebo (-6.40 and -8.71, respectively).

Dr. Ling also performed a sensitivity analysis using an ANCOVA based on the last available observation. She notes that as there were more subjects in the placebo group who lost ambulation or who dropped out and had missing data, and that muscle strength would be likely to continue to deteriorate afterwards in these subjects, this approach would likely yield a more conservative estimate of the treatment effect (albeit still very difficult to interpret given the high degree of missing data). The following table, copied from Dr. Ling's review, summarizes the findings at Year 2 based on this analysis:

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.

Dr. Paine's review provides a summary of the results of the analyses of the secondary endpoints from Study NM-002. However, as he notes, given the small size of the trial, high degree of missing data, and the lack of statistical significance on the primary endpoint analysis, these findings can only be viewed as exploratory and will therefore not be discussed here. That said, as noted above, subjects were discontinued from the trial by design when they lost ambulation, so it is worth considering between group differences in this outcome. In fact, a nominally significant difference was observed with subjects on treatment having a median time to loss of ambulation of 63 months as compared to 31.9 months for placebo (p=0.0052). As Dr. Paine observes, 5 of the 9 dropouts at Year 3 in placebo were due to loss of ambulation as compared to 1 of the 10 deflazacort dropouts at

this time. The median age at the time of loss of ambulation was 146.3 months for the deflazacort arm as compared to 123.6 months for placebo.

Efficacy Conclusions

Study NM-001 demonstrated a highly statistically significant effect on the primary endpoint of change from Baseline on the modified MRC muscle strength measure at Week 12, which is the latest timepoint that allowed for a placebo comparison. This effect was evident in the applicant's MMRM analysis ($p=0.017$ and $p=0.0003$ for the deflazacort 0.9 and 1.2 mg/kg/day arms versus placebo, respectively), and was positive at even lower p-values in Dr. Ling's preferred MMRM analysis ($p=0.047$ and $p<0.0001$ for the deflazacort 0.9 and 1.2 mg/kg/day arms versus placebo, respectively), as well as the ANCOVA approach described in the original study protocol ($p=0.0059$ and $p<0.0001$ for the deflazacort 0.9 and 1.2 mg/kg/day arms versus placebo, respectively). There was a small but consistently greater numerical effect in these analyses in the deflazacort 1.2 mg/kg/day arm as compared to the 0.9 mg/kg/day arm. As Dr. Paine points out, the size of the treatment effect on the modified MRC scale is small; approximately 1/4 to 1/3 of a point on the 11-point scale). However, I agree with his observation that despite these relatively small effects versus placebo at Week 12, the fact that scores on this measure continue to show some improvement over 52 weeks of treatment, as opposed to the expected decline, is further supportive evidence that the effects observed at Week 12 are real and are likely to become more meaningful over time. Unfortunately, the original study protocol did not pre-specify a hierarchy for the analysis of the trial's secondary endpoints. However, although there is some inconsistency in the results of these additional endpoints, I find that the demonstration of highly statistically significant effects on three of the four timed function tests that were evaluated during the trial is additionally supportive of a treatment benefit.

As both Drs. Ling and Paine allude to in their reviews, the interpretation of the results from Study NM-002 is substantially handicapped by its design. Specifically, particularly given the small size of the trial, the fact that subjects were automatically withdrawn when they lost the ability to ambulate led to only 3 placebo patients remaining at Year 2, which was the timepoint for the primary endpoint analysis. However, the nominally significant results on the MRC scale at Month 6 and Year 1 ($p=0.0192$ and $p=0.0056$, respectively), despite a small sample size albeit with lower attrition relative to Year 2, are consistent with the expected treatment effect that would be suggested by the results of Study NM-001. Additionally, the higher incidence of loss of ambulation in the placebo-treated subjects (5/9 dropouts at Year 3 were due to loss of ambulation as compared to 1/10 in the deflazacort arm) can also be considered to be supportive evidence of efficacy. The lack of a pre-specified analytical hierarchy for the trial's secondary endpoints, along with the trial's small sample size, does not permit these results from providing interpretable information.

It is also important to note the fact corticosteroids are considered standard of care for the treatment of DMD worldwide. While anecdotal clinical practice explicitly cannot serve as evidence in support of an approval, the broad experience with these agents in the treatment of DMD does at least provide an additional lens with which to view the efficacy data provided in the current application. Ultimately, despite their limitations, the overall results from Study NM-001 and NM-002 support the conclusion of both Drs. Paine and Ling that efficacy has been established for deflazacort in the treatment of DMD.

A final consideration is the age-range population for which EMFLAZA would be indicated. Although the clinical efficacy trials provided with this application enrolled DMD subjects between ages 5-15

years at Screening, there is no mechanistic reason to expect that EMFLAZA would not also be effective in DMD patients both above and below this age range. However, as is outlined in Section 8 of this memo below, there is no information as to the safety of deflazacort in children younger than 5. Therefore, in the context of this lack of safety information and the absence of definitive evidence of effectiveness in DMD patients below 5 years of age, my recommendation is that EMFLAZA should be indicated only for DMD patients 5 and older. (b) (4)

8. Safety

Dr. Paine conducted the clinical safety review for this application. Data from a total of 319 individuals who have been exposed to deflazacort has been provided in this application, including 135 volunteer subjects (including healthy and hepatically or renally impaired subjects) and 184 DMD subjects (151 from the controlled clinical trials). Of the DMD subjects, 125 have been exposed for greater than 6 months and 62 have been exposed for greater than 1 year. I agree with Dr. Paine that the overall subject exposure is acceptable in the context of the rare nature of DMD.

Dr. Paine found that the applicant's process for recording adverse events (AEs) was appropriate. Dr. Paine's review comments on the limited availability of laboratory assessments from Study NM-001 which mainly consisted of hematology, serum chemistry, and urinalysis at Baseline and at Week 6 (the only timepoint that allows for a comparison to placebo) and Week 24. Dr. Paine notes that analysis of the laboratory data for patients in Study NM-002 was not possible due to missing data.

The following are the key safety results and conclusions that were identified by Dr. Paine in his review:

- There was no clear increase in deaths associated with deflazacort treatment.

- In Study NM-001, the incidence of SAEs was actually lower in the subjects who received deflazacort 0.9 mg/kg/day (2/93; 2.2%) and deflazacort 1.2 mg/kg/day (0/65; 0%) than in those receiving placebo (8/61; 13.1%). Subjects in Study NM-002 who received deflazacort 2/mg/kg every other day had a higher rate of SAEs (8/18; 44%). However, Dr. Paine notes that the greater duration of exposure in this trial contributed to the higher SAE rates in these subjects. Additionally, the most commonly reported SAE was "abasia" which was defined as a loss of ambulation, a universal complication in DMD.

- The following table, produced based on information in Dr. Paine's review, provides a summary of the most frequent (≥ 10% in either of the deflazacort groups) treatment emergent adverse events (TEAEs) in subjects exposed to deflazacort 0.9 and deflazacort 1.2 mg/kg/day, and placebo in Study NM-001:

Preferred Term	Deflazacort 0.9 mg/kg/day (N=93)	Deflazacort 1.2 mg/kg/day (N=65)	Placebo (N=61)
Cushingoid appearance	41 (44.1%)	45 (69.2%)	5 (8.2%)
Erythema	19 (20.4%)	34 (52.3%)	3 (4.9%)
Hirsutism	24 (25.8%)	25 (38.5%)	1 (1.6%)

Weight increased	21 (22.6%)	20 (30.8%)	3 (4.9%)
Headache	17 (18.3%)	22 (33.8%)	12 (19.7%)
Nasopharyngitis	21 (22.6%)	15 (23.1%)	3 (4.9%)
Central obesity	17 (18.3%)	15 (24.6%)	2 (3.3%)
Increased appetite	11 (11.8%)	8 (12.3%)	1 (1.6%)
Pollakiuria	11 (12.9%)	9 (13.8%)	1 (1.6%)
Abdominal pain, upper	9 (9.7%)	9 (13.8%)	4 (6.6%)
Constipation	7 (7.5%)	10 (15.4%)	3 (4.9%)
Upper respiratory tract infections	10 (10.8%)	7 (10.8%)	5 (8.2%)
Influenza	4 (4.3%)	12 (18.5%)	2 (3.3%)
Cough	7 (7.5%)	8 (12.3%)	3 (4.9%)
Rash	5 (5.4%)	7 (10.8%)	3 (4.9%)
Skin striae	4 (4.3%)	8 (12.3%)	0 (0.0%)
Acne	4 (4.3%)	7 (10.8%)	1 (1.6%)
Nausea	4 (4.3%)	7 (10.8%)	2 (3.3%)
Vomiting	2(2.2%)	7 (10.8%)	9 (5.1%)

The TEAEs presented in the preceding table are consistent with the known safety profile of corticosteroids based on extensive clinical experience with the class. Importantly, Dr. Paine concludes that the distinctly higher incidence of TEAEs in the subjects treated with deflazacort 1.2 mg/kg/day, as compared to 0.9 mg/kg/day, justifies the applicant's proposal that only the 0.9 mg/kg/day dose be indicated for the treatment of DMD in the context of a very marginal increase in efficacy at the 1.2 mg/kg/dose.

- Dr. Paine's review also presents findings related to the following AEs of special interest, based on the known safety profile of corticosteroids:

    - Cataracts
    - Psychiatric complications
    - Hypertension
    - Osteoporosis
    - Metabolic abnormalities
    - Effects on growth and development

  TEAEs and/or clinical/laboratory abnormalities related to these categories were observed at higher incidences in the deflazacort-treated subjects when compared to placebo. The observed rates were consistent with the known safety profile of corticosteroids and will be described in the WARNINGS AND PRECAUTIONS section of any approved product labeling, would include updated and comprehensive Agency class labeling language.

- Dr. Paine's review has also revealed 6 cases of Toxic Epidermal Necrolysis (TEN) in the published literature with deflazacort in non-DMD indications, all of which were temporally associated with deflazacort treatment (onset between 2-8 weeks following treatment initiation) and were all reported to resolve with the cessation of therapy. I agree with Dr. Paine's recommendation to include the potential for TEN in the WARNINGS AND PRECAUTIONS section of the label.

- As noted above, interpretable laboratory data was only available at Weeks 6 and 24 from Study NM-001. As subjects only received placebo through Week 12, only the Week 6 data allow for a placebo comparison. Dr. Paine's review notes that at Week 6 in Study NM-001 AST, LDH, and CK levels (all of which were elevated at Baseline consistent with DMD) were increased in placebo, and decreased in the deflazacort-treated subjects. There were trends towards decreases in serum calcium in deflazacort-treatment subjects. Increased excretion of calcium is a known complication of corticosteroid therapy. No other significant differences in laboratory assessments were observed between deflazacort-treated subjects and placebo-treated subjects.

- There were no mean blood pressure differences between deflazacort-treated subjects and placebo-treated subjects. However, Dr. Paine comments that 3 of the outliers with the largest increases in systolic blood pressure from Baseline in Study NM-001 were in the deflazacort 1.2 mg/kg/day arm. One of these subjects had a blood pressure of 198/50 at Week 24. Hypertension is a known adverse reaction associated with corticosteroid therapy.

- Dr. Paine notes that only limited ECG assessments were obtained during the development program. Additionally, the QT-Interdisciplinary Review Team (QT-IRT) reviewer for this application was Dr. Christine Garnett. Dr. Garnett's review concludes that the limited data provided in the application are inadequate to exclude large increases in QTc ≥ 20ms. Therefore, a dedicated QT study to rule out QTc increases ≥ 20 ms is recommended. Dr. Garnett's review acknowledges the feasibility issues of conducting a conventional TQT study for a corticosteroid in healthy individuals or DMD patients, and expresses an openness to alternative designs as discussed in ICH E14 Q&A (R3), Section 6.1. Dr. Garnett defers to the Division as to the acceptability of conducting such a study as a post-marketing requirement, as opposed to a requirement for approval.

- Dr. Paine's review contains a summary of the foreign marketing experience with the Calcort formulation of deflazacort based on the May 17, 2015 United Kingdom (UK) label. The events described therein are consistent with the known safety profile of corticosteroids. A summary of this experience will be reflected in any approved US product label for EMFLAZA.

I agree with Dr. Paine's conclusion that the risks of therapy are acceptable in the context of the potential benefit in the context of the serious nature of DMD. Dr. Paine's review has identified a number of safety concerns, almost all of which are consistent with the well-characterized known safety profile of corticosteroid therapy. The exception being the cases of TEN that have been reported in the published literature but are not currently included in corticosteroid labeling. As already noted, the WARNINGS AND PRECAUTIONS section of the applicant's draft labeling will be revised to be based on updated and comprehensive Agency class labeling language.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable (the target population is pediatric, and discussed in the preceding sections of this memo).

11. Other Relevant Regulatory Issues

- There was limited availability of the original case report forms (CRFs) from the clinical efficacy trials because of the age of the studies. The ability to conduct clinical site inspections was further hampered by the fact that only 3 of the 9 clinical sites from Study NM-001 had sufficient information allowing subjects to be matched with the respective site. Therefore, it was determined that clinical study site inspections would not be conducted for this application.

- No Good Clinical Practice (GCP) issues were identified in Dr. Paine's review.

- The Controlled Substance Staff (CSS) reviewer for this application was Dr. Katherine Bronson. Dr. Bronson's concludes that deflazacort does not have any abuse potential.

- Dr. Paine concludes the applicant has adequately disclosed any financial interests/arrangements with the clinical investigators.

12. Labeling

Please refer to the final negotiated product label. The following are among the key labeling issues that have been considered during this review:

- The recommendation of this review is that Emflaza should be indicated for all DMD patients ages 5 and older.

- The proposed 0.9 mg/kg/day dose for both the oral tablet and oral suspension formulations is acceptable.

- The language in the WARNINGS AND PRECAUTIONS section of the label has been substantially revised to be in line with current Agency thinking for corticosteroid class labeling.

- The CLINICAL STUDIES section of the label has been revised to primarily present the results of the analysis of the primary endpoint from Study NM-001, as this is the only positive finding that was statistically controlled for multiple comparisons. The overall support for this finding from the additional endpoints in Study NM-001, and Study NM-002, will only be briefly presented descriptively at a high level.

13. Postmarketing Recommendations

The Division of Risk Management (DRISK) reviewer for this application is Dr. Robert Pratt. Dr. Pratt concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for EMFLAZA.

The following are the recommended postmarketing requirements:

- A TQT study to evaluate the potential for QTc increases ≥ 20ms. Given the feasibility issues of conducting a conventional TQT study for a corticosteroid in healthy individuals or DMD patients, alternative designs as discussed in ICH E14 Q&A (R3), Section 6.1 would be acceptable, but will need to be discussed with the Agency.

- An oral carcinogenicity study of deflazacort and its major human metabolites in mouse.

- An in vitro bacterial reverse mutation study of major human metabolite 6β-OH-21-desDFZ. The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.

- A study to characterize the deflazacort metabolites circulating in human plasma. For those metabolites circulating at a level greater than 10% of the total exposure to drug and metabolites, characterize the structure and the extent to which each metabolite is present. Include a consideration of the components of metabolite V described in Martinelli et al (Drug Metab Disp 1979; 7:335-339) and in your NDA as having uncertain structure as well as a consideration of metabolite V identified in urine by Huber and Barbuch (Xenobiotica 1995; 25:175-183) that is characterized as a 1,2-epoxy, 3- hydroxy structure.

- A study to characterize the potential for CYP and transporter-mediated interactions due to inhibition or induction of these enzymes and transporters in vitro by the 6β-OH-metabolite (Metabolite III) of deflazacort. Refer to the clinical pharmacology drug interaction guidance for in vitro study design considerations: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

14. Recommended Comments to the Applicant

There are no additional recommended comments for the applicant.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICHOLAS A KOZAUER
02/09/2017