CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	208684/208685
Applicant Name	Marathon Pharmaceuticals, LLC
Date of Submission	June 9, 2016
PDUFA Goal Date	February 9, 2017
Proprietary Name / Established (USAN) Name	Emflaza/deflazacort
Dosage Forms / Strength	0.9 mg/kg/day
Proposed Indication(s)	Duchenne Muscular Dystrophy; Ages 5 (b) (4)
Action/Recommended Action for NME:	Oral tablets (NDA 208684);Oral suspension (NDA 208685)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Rainer Paine
Statistical Review	Xiang Ling
Pharmacology Toxicology Review	Dave Hawver, Lois Freed
OPQ Review	Ray Frankewich, Andrei Ponta, Mark Johnson, Michael Shanks, Yang Zhao, Dahlia A. Woody, Martha Heimann
Clinical Pharmacology Review	Bilal AbuAsal, Atul Bhattaram, Ping Zhao, Kevin Krudys, and Sreedharan Sabarinath
CDTL Review	Nicholas Kozauer
OSE/DMEPA	Ebony Whaley
OSE/DRISK	Bob Pratt
CSS	Katherine Bonson
Office of Study Integrity and Surveillance	Hasan Irier
Patient Labeling Review	Aman Sarai, Aline Moukhtara
Pediatric and Maternal Health Review	Amy M. Taylor
QT review	Dhananjay Marathe

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
OPQ=Office of Pharmaceutical Quality

1. Benefit-Risk Summary and Assessment

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive genetic disorder that causes mutations in the gene that codes for dystrophin, leading to very low levels or complete absence of the protein. Dystrophin, together with a variety of other proteins, maintains the integrity of muscle and its absence leads to replacement of muscle by fibrotic or adipose tissue and progressive loss of ambulation and, eventually, other muscle function (diaphragm, heart). Loss of muscle strength leads first to gait disturbance, generally by 5 years of age, and to loss of ambulation and ability to rise from the ground, generally between 8-16 years, although about 25% of patients are still ambulatory at age 16. Loss of respiratory and cardiac function progress in later years and most patients die in their early to mid-20's of respiratory and/or cardiac failure. DMD has a prevalence of approximately 1 in every 7250 males aged 5-24 years.

There has been great interest in genetic interventions that could increase the amounts of functioning dystrophin, with one product approved in 2016 (eteplirsen, approved under the accelerated approval pathway on the basis of a small increase in muscle dystrophin), but since the 1990's corticosteroids have been used in DMD and have become the standard of care, presumably by treating the inflammatory response that is part of the consequences of diminished dystrophin, although their exact mechanism of action is not known.

Deflazacort (Emflaza) is a new (for the US) corticosteroid, but is approved in many countries in Europe, Asia, and South America for the usual corticosteroid indications (but not for DMD). It is an inactive ester pro-drug that is converted by plasma esterases to its active metabolite, 21-desacatyl-deflazacort (21-desDFZ). 21-desDFZ is metabolized by CYP4503A4 to an inactive metabolite. Dose must be reduced if deflazacort is used with a strong CYP4503A4 inhibitor such as clarithromycin. Deflazacort should not be used with CYP4503A4 inducers, such as rifampin.

The effectiveness of deflazacort in DMD is supported by two well-controlled studies conducted in the 1990's, Study NM-001 and study NM-002.

Study NM-001 was a multicenter randomized, double-blind, placebo-controlled trial conducted in the US and Canada comparing two doses of deflazacort (0.9, 1.2 mg/Kg/day), prednisone 0.75 mg/Kg/day, and placebo in 195 patients. Patients were aged 5-15 and had onset of weakness before age 5. The primary endpoint, change from baseline in average strength of 18 muscle groups, was at 12 weeks, after which placebo patients were randomized to the 3 active treatment groups. All 3 active treatments were statistically significantly superior to placebo at 12 weeks and the higher dose of deflazacort had a numerically larger effect, about 50% larger. This was no longer the case at 52 weeks and the two doses gave very similar results. The lack of any persistent advantage, and the increased rate of corticosteroid adverse effects in the 1.2 mg/Kg/day group, led to the conclusion that only the 0.9 mg/Kg/day dose should be approved. Effects on several additional endpoints (time to stand from the supine position, time to climb 4 stairs, and time to walk or run 30 feet) also favored deflazacort over placebo, supporting the clinical meaningfulness of the muscle effect that was the primary endpoint. These are discussed in detail in the reviews of Drs. Paine and Kozauer.

A second randomized placebo-controlled trial, Study NM-002, was smaller (n = 29). It used a dose of 2 mg/Kg every 2 days, was carried out in patients age 6-12, and also examined average muscle strength. It failed on the primary endpoint at 2 years, as only 3 placebo patients were still in the trial, but showed a significant effect at months 6 and 12 and is clearly supportive.

Risk-Benefit elements are fully discussed in memos by Drs. Bastings, Kozauer, and Paine and I have little to add. Beneficial effects have been shown on the muscle weakness (and its consequences) that is the principal early health consequence of DMD, and deflazacort has the expected risks of any chronically used corticosteroid. The observed risks in Study NM –001 were fairly strikingly dose-related (see below) and will be mitigated by use of the 09 mg/Kg/day dose. I believe the benefits of deflazacort plainly outweigh its risks.

2. Background

As Drs. Paine, Kozauer, and Bastings have noted, DMD is a devastating, X-chromosome linked illness, beginning in childhood (5 years and somewhat older) with devastating progressive loss of muscle function, leading to loss of ambulation and eventually, usually by early 20's, death from loss of respiratory and cardiac function. The only treatments with documented clinical benefit are corticosteroids and deflazacort will be the first member of that class that is FDA-approved for DMD. [redacted] (b) (4) study (NM-001), together with a second trial (NM-002), both of which were acquired by Marathon Pharmaceuticals, is the basis for the current application.

The applicant is proposing both an immediate release tablet (NDA 20684) and an oral suspension (NDA 20865).

3. Product Quality

The Office of Product Quality describes no reservations regarding approval. I concur and have nothing to add.

4. Pharmacology/Toxicology

There were different views as to the adequacy of the non-clinical studies to support approval. Dr. Freed recommends that a mouse carcinogenicity study be a post-marketing requirement if the applicant provides dose-ranging data (post-approval) showing that a carcinogenicity study is feasible. If a carcinogenicity study is not feasible, then a battery of genetic toxicology studies of one major human metabolite (6B-OH-21-desDFZ) should be conducted post-approval. There are also concerns about the lack of data on the in vivo metabolic profile of deflazacort in humans. Post approval studies to further identify and characterize metabolites in humans will be required. Drs. Freed and Bastings believe that the absence of these data should not delay approval.

5. Clinical Pharmacology

The specific product used in the controlled trials supporting the effectiveness of deflazacort was not available so that a direct comparison (bridging) of that product to the to-be-marketed product was not feasible. As explained in section 3.3.6 of the Clin Pharm review, the available evidence supports an "indirect bridge" of the new products to the product tested in trials. In brief, all of the current formulations of deflazacort (oral suspension, tablet, tablet crushed in applesauce) were bioequivalent, suggesting that deflazacort is not sensitive to formulation changes. Deflazacort absorption, moreover, is not affected by pH and GI content. The absorption of deflazacort from the current formulation is > 95% of dose, suggesting little potential sensitivity to formulation differences. Finally, the dose-response curve is relatively flat (0.9, 1.2 mg/Kg/day; 2 mg/Kg/ q2D all being relatively similar), suggesting that small variations in exposure would be unlikely to affect effectiveness. The to-be-marketed formulation is thus likely to have bioavailability similar to the product in studies NM-001 and NM-002. Given the relatively steep dose-response for toxicity and the wide range of body sizes in the treated population, the mg/Kg dosing regimen, rarely used, is appropriate in this case.

As deflazacort is metabolized by CYP4503A4, its blood level can be affected by 3A4 inhibitors and inducers. Labeling will recommend a dose reduction by 2/3 when deflazacort is used with a moderate or strong 3A4 inhibitor and avoidance of moderate or strong 3A4 inducers. No dosing adjustments are recommended for mild to moderate hepatic impairment or renal impairment.

As noted above, further examination of a metabolite of deflazacort (M-V) and other circulating metabolites was recommended and will be required post-marketing.

6. Effectiveness

The effectiveness of deflazacort in improving muscle function was evaluated in two placebo-controlled trials. These are described fully in Dr. Paine's review and in the statistics review of Dr. Ling, and they are discussed by Drs. Kozauer and Bastings.

1. Study MP-104-NM-001 (hereafter NM-001)

Study NM-001 was a randomized, dose response, active and placebo controlled multicenter (sites in U.S. and Canada) trial (1993 – 1995) in 196 patients (all male) with DMD or Beckers MD (almost all had DMD) between the ages of 5 and 15. The study randomized patients to deflazacort at 2 doses (0.9 mg/kg/day, 1.2 mg/Kg/day), prednisone 0.75 mg/Kg/day, and placebo for 12 weeks, stratifying by center and by leg strength. After 12 weeks, placebo patients were randomized to the 3 active treatments for an additional 40 weeks.

Patients at entry had to be male, age 5-15, have had onset of weakness before 5 years old, have had CPK $\geq$ 10 x ULN at some point have, genetic evidence of an abnormal dystrophin gene, and evidence of reduced muscle dystrophin.

The primary endpoint was change from baseline in average muscle strength score over 12 weeks. At each visit (weeks 0, 6, 12) patients had numerous stress tests of shoulder, elbow, knee and other limbs (shown in the following table from Dr. Paine's review), with each test rated on an 11 point-scale (0 – 10). Average muscle strength was the average of all tests performed at a visit and was thus 0-10.

Table 1: Strength testing for the primary endpoint. Testing in parentheses was only done for patients who could not perform movements against gravity.

	Position While Testing Strength					
	Sitting	*Prone*	*Lying on Side*	*Supine*	*(Repeat Lying on Side)*	*(Repeat Sitting)*
Movements tested	Shoulder Abduction	Neck Extension	Hip Abduction	Elbow Extension	(Neck Flexion)	(External Shoulder Rotation)
	Elbow Flexion	Shoulder External Rotation	(Hip Flexion)	Neck Flexion		(Elbow Extension)
	Wrist Flexion	Knee Flexion	(Hip Extension)	(Shoulder Abduction)		
	Wrist Extension	Ankle Plantar Flexion	(Knee Flexion)	(Hip Abduction)		
	Thumb Abduction	Hip Extension	(Knee Extension)			
	Hip Flexion		(Ankle Dorsiflexion)			
	Knee Extension		(Ankle Plantarflexion)			
	Ankle Dorsiflexion		(Neck Extension)			
	Ankle Eversion					
	Ankle Inversion					

There were, in addition, secondary tests, including measures of muscle force, change in timed functional tests (standing from lying position, climbing 4 stairs, running or walking 30 feet), all reasonable measures but hard to interpret as they were not included in a formal statistical analysis plan.

Patients' average age in all groups were 8.5-8.8 years, but all groups ranged from 5-15. Baseline characteristics are shown in the following table.

Table 2: Baseline Characteristics of Study Groups in Safety Population (Source: NM-001 Study Report Body, p. 56)

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
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)
Median	6.03	6.31	6.47	6.38	6.31
Min, Max	2.3, 9.0	2.5, 8.9	2.2, 9.8	3.6, 8.7	2.2, 9.8
Pulmonary Function Testing – FVC (liters)					
n	50	48	46	47	191
Mean (SD)	1.378 (0.4982)	1.321 (0.5964)	1.423 (0.6242)	1.373 (0.5342)	1.373 (0.5609)
Median	1.293	1.230	1.243	1.270	1.260
Min, Max	0.49, 2.72	0.47, 3.12	0.61, 3.32	0.67, 3.13	0.47, 3.32
Pulmonary Function Testing – MVV (liters/minute)					
n	49	48	45	47	189
Mean (SD)	37.606 (13.8856)	37.632 (19.3069)	37.897 (20.1686)	39.474 (22.7278)	38.146 (19.0947)
Median	35.500	32.000	33.000	33.500	33.500
Min, Max	11.65, 67.75	11.20, 98.00	11.00, 119.30	9.25, 139.45	9.25, 139.45
Timed-Functional Testing – Standing from Lying Supine (seconds)					
n	25	27	27	30	109
Mean (SD)	7.57 (4.926)	8.21 (5.669)	5.86 (2.845)	8.20 (4.570)	7.48 (4.650)
Median	6.35	6.35	5.40	7.10	6.35
Min, Max	2.5, 19.0	0.0, 26.3	1.7, 13.0	2.0, 24.5	0.0, 26.3
Timed-Functional Testing – Climbing 4 stairs (seconds)					
n	29	32	31	33	125
Mean (SD)	6.84 (6.607)	8.36 (8.902)	8.50 (14.109)	6.45 (4.847)	7.54 (9.205)
Median	4.85	5.75	4.30	5.25	4.85
Min, Max	1.7, 31.2	0.0, 48.3	1.0, 59.8	1.4, 24.3	0.0, 59.8

Results at 12 weeks on muscle strength are shown in Dr. Paine's table (sponsor's analysis) below. Dr. Ling performed other analyses (MMRM, ANCOVA), finding somewhat lower p-values, but reaching the same conclusions, viz, that deflazacort improved muscle strength at 12 weeks. At 12 weeks both deflazacort 1.2 mg/Kg/day and prednisone appeared numerically superior to deflazacort 0.9 mg/Kg/day.

Table 3: NM-001 Primary Endpoint Results (Source: NM-001 Body, p. 59)

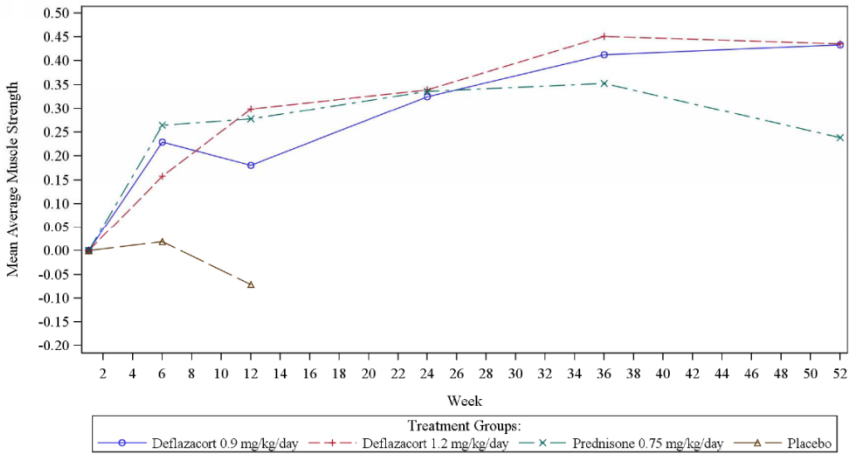
Visit	Treatment	N	n	Change from Strength [a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Active - Placebo	95% CI	P-value
Week 12	Deflazacort 0.9 mg/kg/day	51	48	0.15 (0.01, 0.28)	0.25	(0.04, 0.46)	0.0173
	Deflazacort 1.2 mg/kg/day	49	46	0.26 (0.12, 0.40)	0.36	(0.14, 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)	-	-	-

Reference: Table 14.2.1.1
Abbreviations: CI=confidence interval; LS=least squares; n=number of observations;
N=number of patients. Note: Baseline was the average of Visit 1 and Visit 2 measurements.

[a] Analysis results are from a mixed model of repeated measurements. The model included treatment group, visit, treatment by visit, stratum, and site as fixed effects. The baseline value was included as a continuous covariate. P-values and confidence limits are based on the Dunnett technique.

The difference between deflazacort 0.9 and 1.2 mg/Kg/day is described repeatedly in reviews as small but numerically it is 50% greater, not obviously trivial. Despite the increased rate of adverse effects at the higher dose, I initially thought it should be considered, with appropriate warnings. Dr. Ling's analysis of the 52 week data (figure below), however, strongly argues against that.

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



With longer dosing, and multiple measurements, the two doses of deflazacort appeared to have essentially identical effects, and appeared better than prednisone. Given the increased toxicity and absence of long-term advantage there seems no reason to use a dose greater than 0.9 mg/Kg/day.

The additional endpoint results are described by Drs. Paine and Kozauer, and included pulmonary function tests and timed function testing some of which seemed clinically meaningful with very small nominal p-values, as described by Dr. Kozauer.

- 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.

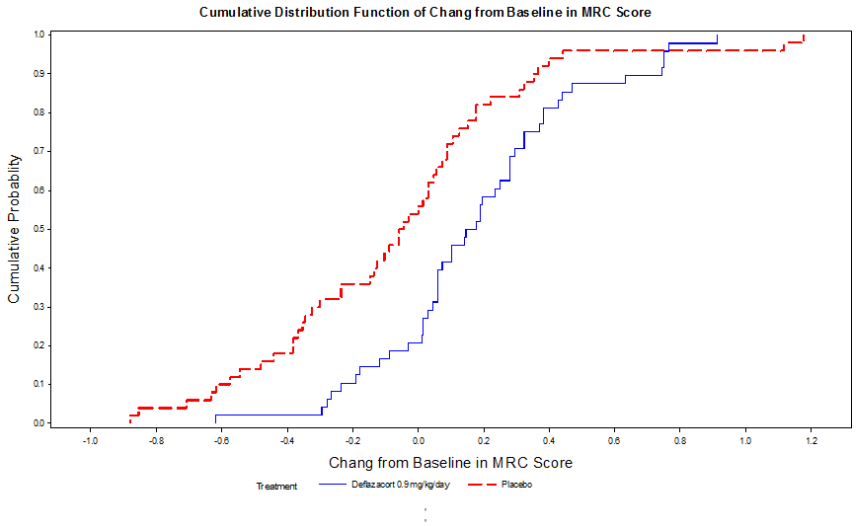
Dr. Ling examined the change from baseline at week 12 for patients 5-9 and > 9, each about 50% of the patient population. Effect size may have been somewhat larger in the older patients, but differences were small.

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	0.2	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	0.3	0.46	0.34	-
95% CI	(0.095, 0.518)	(0.236, 0.677)	(0.114, 0.566)	-

Source: FDA reviewer.

The overall mean effect on strength, about 0.3 more than placebo on a 10 point scale, is modest. It is usually useful to examine the distribution of results, which are shown in the following figure provided by Dr. Bastings. There were clearly some patients (about 25%) with effect sizes (vs baseline) of 0.4-0.5 points on deflazacort, but very few on placebo, and over 75% of patients, improved on deflazacort, vs about 50% on placebo.



2. Study NM-002

A second controlled trial NM-002 was carried out in Italy before 1988 and 1991. It was a placebo-controlled multi-center study in 29 ambulatory male patients, aged 5-11 years with 2:1 randomization to deflazacort 2 mg/Kg every 2 days, or placebo. The endpoint was change in muscle strength from baseline to year 2. Patients were to remain in the study for 2 years or until loss of ambulation. The muscle strength score is described in reviews of Drs. Paine and Kozauer.

The analysis was not clearly pre-specified, as discussed by Dr. Ling, and the 2-year evaluation was rendered uninterpretable by loss of almost all placebo patients by 2 years because of loss of ambulation. Analysis by Dr. Ling, using the last available observation, showed a significant effect on preservation of muscle strength and analyses by the sponsor of 6 month and year one data, when most patients were still in the study, also showed a significant effect, as shown in Dr. Ling's review.

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. Bastings also notes, a nominally significant difference was seen in median time to loss of ambulation, 63 months deflazacort vs 32 months for placebo (p = 0.0052).

As Drs. Paine, Kozauer, Bastings, and Ling have concluded, Study NM-001clearly demonstrates effectiveness and this is supported by Study NM-002, despite some of the uncertainties in statistical plans. The timed function tests, as Dr. Kozauer notes, are also supportive and will be briefly cited in section 14 of labeling. There are too few data in DMD subjects below 5 to endorse use in that population and labeling will indicate the drug for patients at least 5 years old.

7. Safety

I have nothing at all to add to the extensive safety discussion of Drs. Paine, Kozauer, and Bastings. The adverse effects seen are those expected of a corticosteroid, as described in all clinical reviews. These are shown in the table below.

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 increased rate of many AEs in the deflazacort 1.2 mg/Kg/day group is fairly striking and somewhat surprising given the small difference from 0.9 mg/Kg/day. As noted above, the loss of any larger effect of the higher dose over time convinced me that, as all other reviewers believe, the higher dose is not needed. The steep toxicity dose-response relationship supports the weight-based dosing recommendation.

Overall exposure (319 patients) was adequate for a member of a well-studied class of drugs in an orphan disease, and with extensive marketing experience, but there will be post-approval requirements for additional studies of possible metabolites and of QT effects. Published literature cites 6 cases of Toxic Epidermal Necrolysis (TEN), convincingly related to deflazacort, and this will be noted in Warnings and Precautions.

The benefits of deflazacort in treatment of DMD clearly outweigh its risks.

8. Advisory Committee

   No advisory committee meeting was considered to be needed.

9. Pediatrics

   The approval letter will include a written request for a study of patients < 5 years old.

10. Post-marketing requests

    As detailed by Dr. Bastings the approval letter will require the applicant to:

    a. Conduct a mouse oral carcinogenicity study of deflazacort and major human metabolites.
    b. Characterize the deflazacort metabolites circulating in human plasma.
    c. Assess potential for effects on CYP and transporter-mediated interactions of Metabolite III of deflazacort.
    d. Conduct a clinical trial to assess the risk of QT prolongation.
    e. If an oral carcinogenicity study is not feasible, conduct an in vitro bacterial reverse mutation study of major human metabolite 6B-OH-21-desDF2, an in vitro rodent bone marrow micronucleus study of the same metabolite, and an in vitro mammalian chromosomal aberration study of the same metabolite.

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

/s/

ROBERT TEMPLE
02/09/2017