CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208684 and 208685
Priority or Standard	Priority
Submit Date(s)	6/9/2016
Received Date(s)	6/9/2016
PDUFA Goal Date	2/9/2017
Division/Office	DNP/OND
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Addendum Date	2/15/2017
Established Name	Deflazacort
(Proposed) Trade Name	Emflaza
Applicant	Marathon Pharmaceuticals, LLC
Formulation(s)	Oral tablets (NDA 208684); Oral suspension (NDA 208685)
Dosing Regimen	0.9 mg/kg/day once daily
Applicant Proposed Indication(s)/Population(s)	Duchenne muscular dystrophy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Duchenne muscular dystrophy

Erratum:

Table 2 on page 33 of the clinical safety and efficacy review erroneously states that the latter 40 weeks of Study MP-104-NM-001 (Study 1 in the Emflaza label) were open-label. As consistently described in the protocol (p. 21) and clinical study report (p. 26), placebo patients from the first 12 weeks of the study were randomized in a double-blind fashion to one of the three active treatment groups for the latter 40 weeks of the study. The blind for the patients already in an active treatment group was maintained for the final 40 weeks of the study.

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/s/

RAINER PAINE
02/15/2017
ADDENDUM TO CLINICAL REVIEW

NICHOLAS A KOZAUER
02/15/2017

CLINICAL REVIEW

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Application Number(s)	208684 and 208685
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Established Name	Deflazacort
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Glossary

AC	advisory committee
AE	adverse event
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BMD	Becker Muscular Dystrophy
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CSR	Clinical Study Report
CK	Creatine Kinase
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DMD	Duchenne Muscular Dystrophy
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Deflazacort (Emflaza™) is a glucocorticoid that has been used as an anti-inflammatory and immunosuppressive agent. It has international approvals under various names (Calcort, Cortax, Decortil, Deflanil) for multiple autoimmune conditions and hypersensitivity reactions in the United Kingdom, Switzerland, Spain, Germany, Greece, Italy, Portugal, Mexico, Central & South America, the Caribbean, India, and South Korea.

The applicant proposes two forms of deflazacort, an oral tablet under NDA 208684 and an oral suspension under NDA 208685, for the treatment of Duchenne muscular dystrophy (DMD). Deflazacort has not been previously approved for DMD in any country. The applicant proposes an oral daily dosing regimen of 0.9mg/kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence of effectiveness in DMD stems from two double-blind, randomized, multi-center placebo-controlled clinical studies, MP-104-NM-001 and MP-104-NM-002, referred to in this text as studies NM-001 and NM-002, respectively. These studies evaluated the use of deflazacort versus placebo in pediatric DMD patients by assessing measures of strength over time, as well as other assessments such as timed functional testing and metabolic markers of muscle injury.

Summary of Results

Study NM-001 was an adequate and well-controlled clinical investigation which showed that mean strength increased slightly (~2-3%) in both the 0.9 and 1.2 mg/kg/day deflazacort groups compared to a small (<1%) decrease in strength over the 12 week placebo arm of the study. There was a statistically significant difference in the 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: $p = 0.0003$) compared to placebo. For both deflazacort doses, the mean muscle strength continued to trend upwards beyond the 12-week placebo-control period to study completion at 52 weeks, at which time there was an approximate 5% improvement in mean

strength compared to baseline (4% for the 1.2mg/kg dose and 6% for the 0.9mg/kg dose).

Although study NM-002 had a negative finding for the primary endpoint at year 2, the loss of most placebo patients from the study at year 2 makes the primary endpoint result unclear. Positive results at year 1 combined with the results of the secondary endpoint analyses provide confirmatory evidence to support the results of study NM-001. In study NM-002, the deflazacort 2mg/kg alternating day dose had an approximate 2% drop in mean strength over 12 months compared to an approximate 4% decrease in mean strength in the 12 month placebo arm. Timed functional tests also supported the efficacy of deflazacort with reductions in time to standing, 4 stair climbing time, and 30 ft. walk time. Decreases in metabolic markers of muscle injury were also supportive of a benefit from deflazacort, with decreases in ALT, CK, and LDH by week 6 of treatment with deflazacort compared to increased levels in the placebo group. There is also an interesting finding from study NM-002 that 8/11 (~73%) of DMD patients in the placebo group lost ambulation compared to 5/18 (28%) in the deflazacort group, suggesting that deflazacort might help maintain ambulation in DMD patients. The mean and median ages at the time of loss of ambulation were more than 20 months later for the deflazacort group compared with the placebo group, providing further evidence that deflazacort may have a beneficial effect in delaying the loss of ambulation. Note that this finding is consistent with reports in the literature that deflazacort may delay the age at loss of ambulation by 1.4–2.5 years (Gloss et al., 2016). Taken together, these results support the conclusion that deflazacort can provide a meaningful clinical benefit to patients with DMD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Deflazacort (EMFLAZA) is an inactive, ester pro-drug which is metabolized rapidly to the active drug 21-desacetyldeflazacort (21-desDFZ). Deflazacort is a glucocorticoid, a class of corticosteroid, that is currently used in multiple foreign countries for its anti-inflammatory and immunosuppressive effects.

Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive muscle disorder that leads to loss of ambulation, cardiac and respiratory failure, and death typically by 30 years of age. The disease affects approximately 1 in 3600-6000 male births and has a prevalence of approximately 1 in every 7,250 males aged 5 – 24 years (Romitti et al., 2015).

Treatment has been limited to corticosteroids and supportive care. One drug, eteplirsen, was approved by the FDA via the accelerated approval pathway for the treatment of patients with DMD caused by mutations that are amendable to exon 51 skipping in 2016 based on an increase in muscle dystrophin. The clinical effectiveness of eteplirsen has not been established.

Evidence from clinical trials indicates that deflazacort improves the muscle strength of DMD patients, slows the loss of strength over time, and improves the ability to accomplish tasks related to activities of daily living such as standing up, walking, and climbing stairs. Less clear evidence suggests that deflazacort may also delay the loss of the ability to walk. The clinical studies reviewed did not provide any evidence for or against a change in the longevity of DMD patients treated with deflazacort.

Deflazacort carries the many risks associated with the class of corticosteroids, including Cushing syndrome and potentially life-threatening adrenal crisis if treatment is stopped suddenly. 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%). The adverse event that caused the most patients to stop taking deflazacort was weight gain. Increased weight could further limit mobility in DMD patients.

As with other corticosteroids, patients treated with deflazacort appear to be more susceptible to infectious disease due to immunosuppression, as indicated by the increased rates of upper respiratory tract infections and influenza in the deflazacort arms of the clinical studies. One study

patient treated with deflazacort developed a life-threatening encephalitis with psychotic symptoms.

Corticosteroids are known to cause elevations in blood pressure. Although there did not appear to be a trend toward hypertension in the studied patients, one deflazacort study patient had an urgent hypertensive crisis.

Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids. A range of psychiatric adverse events were reported at a greater rate in the deflazacort groups compared to placebo: abnormal behavior (6.8% vs. 4.9% placebo), irritability (5.1% vs. 3.3% placebo), aggression (4% vs. 1.6% placebo), psychomotor hyperactivity (4% vs. 1.6% placebo), affect lability (2.3% vs. 0% placebo), and mania (0.6% vs. 0% placebo).

There are case reports in the medical literature of toxic epidermal necrolysis (TENS), a life-threatening skin condition, related to deflazacort use. Although this condition was not seen in the clinical studies of deflazacort, treatment with deflazacort should be stopped if signs of TENS develop.

The conclusion of this review is that substantial evidence of clinical efficacy has been established for the treatment of DMD with deflazacort. Although deflazacort, like other corticosteroids, has numerous potential adverse effects, the potential benefit of improved quality of life through increased strength and mobility for DMD patients outweighs the risks given the severely debilitating and terminal nature of the disease. Patients and their physicians should monitor side effects during treatment and taper the deflazacort dose slowly if the side effects become intolerable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive muscle disorder that leads to loss of ambulation, cardiac and respiratory failure, and death typically by 30 years of age. The disease affects approximately 1 in 3600-6000 male births and has a prevalence of	DMD is a terminal disease that progressively weakens and immobilizes children and young adults. Death usually results from cardiac and respiratory complications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	approximately 1 in every 7,250 males aged 5 – 24 years (Romitti et al., 2015).	
Current Treatment Options	The current standard of care is corticosteroids (glucocorticoids such as prednisone, prednisolone, and deflazacort) with supportive care such as such as assisted ventilation and physiotherapy. Deflazacort is not currently available for sale in the United States. One drug, eteplirsen, was approved by the FDA via the accelerated approval pathway for the treatment of patients with DMD mutations that are amendable to exon 51 skipping in 2016. The risks of chronic corticosteroid use include Cushing syndrome, increased infections, diabetes, delayed puberty, behavioral changes, obesity, cataracts, osteoporosis, and increased frequency of long bone and vertebral fractures.	Patients suffering from DMD face a terminal prognosis. There is an unmet need for effective treatments for DMD.
Benefit	Deflazacort (EMFLAZA) is an inactive, ester pro-drug which is metabolized rapidly to the active drug 21-desacetyldeflazacort (21-desDFZ). Deflazacort is a glucocorticoid, a class of corticosteroid, that is currently used in multiple foreign countries for its anti-inflammatory and immunosuppressive effects. Clinical trial evidence indicates that deflazacort improves the muscle strength of DMD patients. In a 12-week double-blind placebo-control study, mean muscle strength increased slightly (~2-3%) in both the 0.9 and 1.2 mg/kg/day deflazacort groups compared to a small (<1%) decrease in strength in the patients who received placebo. There was a statistically significant difference in the change in muscle strength score from baseline to week 12 n favor of the two deflazacort groups	Based on the clinical study results, deflazacort can improve DMD patients' quality of life by improving muscle strength, increasing the ease of daily tasks such as standing up, walking, and climbing stairs, and possibly delaying the loss of the ability to walk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(0.9 mg/kg/day: p = 0.0173; 1.2 mg/kg/day: p = 0.0003) compared to placebo. For both deflazacort doses, the muscle strength continued to trend upwards beyond the 12-week placebo-control period to study completion at 52 weeks, at which time there was an approximate 5% improvement in strength compared to baseline for both deflazacort doses. There is nominally significant evidence that deflazacort also reduces the time it takes for DMD patients to stand up (p = 0.0018, 0.0002 for deflazacort 0.9 and 1.2mg/kg versus placebo, respectively), walk 30 feet (p < 0.0001 for both deflazacort 0.9 and 1.2mg/kg), and climb four stairs (p < 0.0001 for both deflazacort 0.9 and 1.2mg/kg). In a second double-blind placebo-control study of deflazacort 2mg/kg taken every other day, mean strength decreased by approximately 2% over 12 months in the deflazacort group compared to an approximate 4% decrease in strength in the placebo group. Strength assessments performed following 6 months and 12 months showed nominally significant between-treatment differences in change from baseline between the placebo and 2mg/kg alternating day deflazacort groups of 6.97 (95% CI [1.24, 12.69], p = 0.0192) and 8.53 (95% CI [2.75, 14.32], p = 0.0056), respectively. Nominally significant evidence also suggests that deflazacort may delay the loss of the ability to walk in DMD patients (median of 63.0 months for the deflazacort group versus 31.9 months for placebo, p =	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	0.0052).	
Risk	Deflazacort carries the multiple risks associated with the class of corticosteroids, including Cushing syndrome and potentially life-threatening adrenal crisis if treatment is stopped suddenly. 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% vs. 4.9% placebo), irritability (5.1% vs. 3.3% placebo), aggression (4% vs. 1.6% placebo), psychomotor hyperactivity (4% vs. 1.6% placebo), affect lability (2.3% vs. 0% placebo), and mania (0.6% vs. 0% placebo). There are case reports in the medical literature of toxic epidermal necrolysis (TENS), a life-threatening skin condition, related to deflazacort use. This condition was not seen in the clinical studies of deflazacort.	Although deflazacort, like other corticosteroids, has numerous potential adverse effects, the potential benefit for DMD patients outweighs the risks given the terminal nature of the disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	Corticosteroids, including deflazacort, have many potential adverse effects, such as potentially life-threatening adrenal crisis if treatment is stopped suddenly. Product labeling should include both the adverse events seen in deflazacort clinical studies as well as warnings based on the known risks associated with the class of corticosteroids.	Patients and their physicians should monitor side effects during treatment and taper the deflazacort dose slowly if the side effects become intolerable. The risks associated with deflazacort use can be addressed through the use of clear labeling, as has been the case for corticosteroids approved for numerous other conditions in the US.

2 Therapeutic Context

2.1. Analysis of Condition

Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive muscle disorder due to mutations in the DMD (dystrophin) gene that leads to loss of ambulation, cardiac and respiratory failure, and death typically by age 30 despite treatment. The disease affects approximately 1 in 3600-6000 male births and has a prevalence of approximately 1 in every 7,250 males aged 5 – 24 years (Romitti et al., 2015). It is the most common and most severe form of muscular dystrophy.

Female manifesting carriers are rare. Between 2.5 and 17% of carriers can show mild muscle weakness or even a DMD-like muscular dystrophy. Carriers are also at increased risk of cardiomyopathy.

Boys present with symptoms such as abnormal gait and proximal weakness between the ages of 3 and 5 years. Patients often have difficulty climbing stairs, hopping, or arising from the floor, as well as cognitive impairment. Some signs of the disease may be present in infancy, although most parents only become aware of them retrospectively.

The clinical course is characterized by a developmental improvement in strength until about age 6 or 7, a plateau phase lasting up to 18 months, followed by progressive decline. Without treatment, ambulation is usually lost by age 12. Following the loss of ambulation, there is progressive loss of arm movements, increasing respiratory insufficiency and scoliosis, and cardiomyopathy. Without treatment, death usually occurs by age 20 years due to respiratory failure and cardiomyopathy.

Diagnosis can be made through a combination of family history, clinical features, laboratory markers (elevated serum creatine kinase (CK)), muscle histopathology, and genetic analysis. Newborn screening is available based on elevated CK levels and DNA mutational analysis (Hilton-Jones & Turner, 2014).

2.2. Analysis of Current Treatment Options

Treatment for DMD has generally been limited to corticosteroids and supportive care.

The American Academy of Neurology (AAN) practice guideline (Gloss et al., 2016) for corticosteroid treatment of Duchenne muscular dystrophy recommends prednisone and deflazacort as therapy for DMD. There are varying degrees of reported evidence that prednisone may improve strength, pulmonary function, timed motor function, may reduce the need for scoliosis surgery, and delay cardiomyopathy onset. Published studies suggest that deflazacort may improve strength and timed motor function, delay the age at loss of ambulation by up to 3 years or more, improve pulmonary function, reduce the need for scoliosis surgery, delay cardiomyopathy onset, and increase survival at 5–15 years of follow-up.

Corticosteroids have numerous adverse effects, such as Cushing syndrome and adrenal crisis upon acute withdrawal, that limit their long-term use and tolerability. Published studies suggest that prednisone may be associated with greater weight gain in the first years of treatment than deflazacort. Deflazacort may be associated with a greater risk of cataracts than prednisone. Prednisone is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Gloss et al., 2016).

Supportive care may include physical therapy, orthopedic appliances such as braces and wheelchairs, as well as appropriate cardiac, respiratory, nutritional, and mental health support.

The only FDA-approved treatment for DMD, eteplirsen, was recently approved in 2016. Eteplirsen was approved using the accelerated approval pathway based on a small increase in dystrophin production in patients with DMD caused by mutations that are amendable to exon 51 skipping. Clinical efficacy of eteplirsen has not been established.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Deflazacort has not previously been marketed in the United States, although it has multiple international approvals discussed in Section 3.3. Deflazacort (b) (4) has received Orphan Drug Designation (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The initial IND 119258 for deflazacort for DMD by Marathon Pharmaceuticals was submitted in October of 2014. The Agency granted Orphan Drug designation to deflazacort for the treatment of DMD on August 16, 2013, and Fast Track designation on November 21, 2014. Marathon requested Rare Pediatric Disease designation on March 20, 2015, which was granted on August 10, 2015.

A Type B, pre-NDA meeting was held on August 4, 2015 where it proposed submitting a marketing application based on data from trials conducted in the early 1990's. During that meeting it was noted that 5 patients lacked case report forms but still had data available from source documents. The Division also stated that it was not clear if full approval would be adequately supported by short-term muscle strength findings, which were the primary endpoints in the trials, and that results from secondary endpoints (arm and leg function, timed function tests and pulmonary function) may be useful to establish clinical benefit.

Deflazacort was granted a priority review designation for this application.

3.3. Foreign Regulatory Actions and Marketing History

Deflazacort has international approvals for a wide range of conditions, such as autoimmune diseases and hypersensitivity reactions, that are responsive to glucocorticoids in the United Kingdom (2008), Switzerland (2013), Spain (1990), Germany, Greece, Italy, Portugal, Mexico, Central & South America, the Caribbean, India, and South Korea. Deflazacort is not approved for any indication in the United States. There is no prior approval for DMD in any country.

Sanofi markets the drug under the trade name Calcort® in the United Kingdom, Switzerland, and countries in Latin America and the Caribbean islands. The drug is also available generically in markets such as Germany, Greece, Italy, Portugal, and Spain.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

As stated in Section 3.2, there was limited availability of original Case Report Forms due to the age of the clinical studies, although the data were still available from source documents. The ability to conduct study site visits was hampered by the loss of information matching subjects to study sites. Subjects could be matched to clinical trial sites for only 3 of the 9 sites for the key efficacy study NM-001. Therefore, it was determined that clinical study site inspections would not be conducted for this application.

4.2. Product Quality

The two clinical efficacy studies (MP-104-NM-001 and MP-104-NM-002) were conducted approximately 25 years ago with Sanofi's formulation of deflazacort (Calcort brand). Deflazacort immediate release tablets, containing 6, 18, 30, or 36 mg deflazacort, and a deflazacort suspension, 22.75 mg/mL, were developed for use in the applicant's clinical development program.

A relative bioavailability study (Marathon Study MP-104-CL-058) was conducted to compare the current Sanofi Calcort tablet formulation (6 x 6 mg) to Marathon's highest-strength tablet formulation (36 mg) intended for commercial distribution. The applicant states that the formulations were bioequivalent. *Analysis and discussion of the acceptability of this study is deferred to the chemistry, manufacturing, and controls (CMC) reviewer.*

4.3. Clinical Microbiology

Not applicable. Deflazacort is not an antimicrobial or antiviral drug.

4.4. Nonclinical Pharmacology/Toxicology

The applicant did not conduct any acute toxicology studies with deflazacort and cited literature reports that the lethal dose, 50% for the oral dose in laboratory animals is > 4000 mg/kg.

The applicant conducted both in vitro and in vivo (rat and monkey) repeat-dose toxicity trials to characterize the effects of deflazacort and its metabolite 21-desDFZ. During Study MP-104-NC-036 deflazacort was administered to Sprague-Dawley rats via oral gavage once daily for 26 weeks at a dose level of 0.05, 0.15, or 0.50 mg/kg/day (males) or 0.10, 0.30, or 1.00 mg/kg/day (females). Treatment resulted in skin lesions (discolored hair coat, skin alopecia, skin scab, and skin discoloration) and behavior changes (hyperactivity and/or increased reactivity to stimulus); decreased body weight gains for males administered ≥ 0.05 mg/kg/day and females administered ≥ 0.10 mg/kg/day; and decreased food consumption for males administered ≥ 0.05 mg/kg/day and females administered 1.00 mg/kg/day.

The applicant did not conduct any carcinogenicity studies with deflazacort. The applicant states that at the pre-Investigational New Drug (IND) meeting with the Agency it was agreed that such

studies, if required, could be conducted as a Phase 4 commitment.

The applicant states that three nonclinical studies (MP-104-NC-030 , -036, and -039) contained male reproductive and developmental toxicity endpoints in assessing deflazacort administered to either rats or monkeys, with no deflazacort-related testicular lesions or changes in sperm parameters (Nonclinical overview, p. 29).

Analysis and determination of the acceptability of nonclinical studies is deferred to the nonclinical reviewer.

4.5. Clinical Pharmacology

Deflazacort is an inactive, ester pro-drug which is metabolized rapidly to the active drug 21-desacetyldeflazacort (21-desDFZ). The equipotency ratio between deflazacort and prednisone has been reported as approximately 1.3:1 (DFZ:Pred) which calculates to deflazacort potency of about 75% that of prednisone. A summary of the in vitro and in vivo clinical pharmacology studies for deflazacort based on the submission is presented in the following table.

Table 1: Clinical Pharmacology Studies for Deflazacort (Source: Summary of Clinical Pharmacology, p. 12)

Type of study	Identifier	Study Design	Study Medication and Dosing	Number and Type of Subjects	Duration of Treatment
In vitro	MP-104-NC-012	In vitro cytochrome CYP450 reaction assay	21-desDFZ, 1 µM	Human CYP450 enzyme isoforms	5, 10, 20, 30 or 60 minutes, 37°C
In vitro	MP-104-NC-043	In vitro drug metabolism assay (CYP induction)	21-desDFZ, 0.01, 0.1, 1, or 10 µM	Human CYP450 isoforms	Overnight, Days 3 to 6 (72 hours), 37°C
In vitro	MP-104-NC-044	In vitro CYP inhibition (IC_{50}) assay	21-desDFZ, 0.0457, 0.137, 0.412, 1.23, 3.70, 11.1, 33.3 or 100 µM	Human CYP450 isoforms	30 minutes, 37°C
In vitro	MP-104-NC-045	In vitro inhibition	21-desDFZ, 1 or 10 µM	HEK293 transfected	Substrate assay:

		(OATP1B1, OATP1B3) and substrate (OATP1B1, OATP1B3, OAT1, OAT3 and OCT2) assays	(substrate assay) 0.4 µM to 100 µM, at 6 concentrations using a 3-fold dilution scheme (inhibition assay)	with human SLC transporters	2 or 20 minutes, 37°C Inhibition assay: 2, 3 or 5 minutes, 37°C
In vitro	MP-104-NC-046	In vitro UGT drug inhibition assay	21-desDFZ 0.0457, 0.137, 0.412, 1.23, 3.70, 11.1, 33.3 or 100 µM	Recombinant UGT enzymes	30 ± 2 minutes (20 ± 2 minutes for UGT1A4), 37°C
In vitro	MP-104-NC-047	In vitro UGT drug substrate assay	21-desDFZ, 20 µM	recombinant UGT enzymes	15, 30 or 60 minutes
In vitro	MP-104-NC-054	In vitro plasma protein binding assay	21desDFZ, 5 µM	HSA and/or AAG	4 hours, 37°C
In vitro	MP-104-NC-055	In vitro Pgp and BCRP inhibition and substrate assays	Substrate assay: Deflazacort or 21-desDFZ, 10 µM Inhibition assay: 0.4-100 µM	Substrate assay: MDCK epithelial (Pgp) or Caco-2 (BCRP) cell lines	2 hours both assays 37°C for inhibition assay
PK	MP-104-CL-005	Open-label, single-period, single-dose, multicenter, nonrandomized, phase 1	Oral deflazacort 6 mg tablets	24 patients with DMD	8 days
PK	MP-104-CL-023	Open-label, single-dose, multicenter, nonrandomized, phase 1	Oral deflazacort 6 x 6 mg tablets	16 healthy subjects	1 day
PK	MP-104-CL-024	Open-label, single-dose, multicenter, nonrandomized, phase 1	Oral deflazacort 6 x 6 mg tablets	16 healthy subjects	1 day
PK	MP-104-CL-025	Open-label, parallel 2-arm, 2-period,	Oral deflazacort 3 x 6 mg tablets Single-dose on	58 healthy subjects	2 nonconsecutive days for

		fixed-sequence, randomized, phase 1	Day 1; Oral rifampin 2 x 300 mg capsules every 24 hours for 10 days, with 3 x 6 mg deflazacort tablets co-administered on Day 10;		deflazacort; 10 days for rifampin; 4 days for clarithromycin
BE/Food effect	MP-104-CL-026	Open-label, randomized, 5-period, phase 1, crossover, single-center, single-dose	A) Oral deflazacort 36 mg tablet, fasted B) Oral deflazacort 36 mg tablet, high-fat meal C) Oral deflazacort 36 mg crushed tablet in applesauce, fasted D) Oral deflazacort 6 x 6 mg tablets, fasted E) Oral deflazacort 36 mg suspension in apple juice, fasted	45 healthy subjects	1 day
BA	MP-104-CL-058 Open-label,	Open-label, single-dose, randomized, 2-period, single-center, phase 1, crossover	Oral deflazacort 36 mg (1 x 36 mg, Marathon's proposed formulation) tablets (Treatment A), Calcort (deflazacort) 36 mg (6 x 6 mg) tablets	50 healthy subjects	1 day

			(Treatment B)		
Population PK	MP-104-NC-063	Pooled PK analysis (MP-104-CL-005, MP-104-CL-023, MP-104-CL-024, MP-104-CL-025, MP-104-CL-026)	Oral deflazacort 6 mg tablets (various doses; 18 or 36 mg)	159 subjects	Various durations; refer to data for individual studies
PBPK Model	MP-104-NC-062	PBPK pooled simulation (MP-104-CL-023, MP-104-CL-024, MP-104-CL-025)	Oral deflazacort 6 mg tablets (various doses; 18 or 36 mg) 0.9 mg/kg/day (0.8 mg/kg/day) for pediatric subjects	Healthy subjects (from studies mentioned and simulated data)	Various durations; refer to data for individual studies

4.5.1. Mechanism of Action

Deflazacort is a glucocorticoid used as an anti-inflammatory and immunosuppressive agent. It may decrease inflammation and fibrosis in muscles affected by DMD. Glucocorticoids bind to glucocorticoid receptors (GR) and up-regulate the expression of anti-inflammatory proteins while repressing the expression of pro-inflammatory proteins in the cytosol. The primary pharmacology of deflazacort includes binding to GRs, up regulation of anti-inflammatory and immunosuppressant activity, with an effect on muscle injury and muscle repair that is similar to other glucocorticoids (Clinical Overview, p. 23).

4.5.2. Pharmacodynamics

No formal exposure-response relationship has been established for deflazacort in the DMD patient population. The applicant states that study MP-104-NM-001 established a dose-response relationship wherein the efficacy at 1.2 mg/kg/day was only marginally better than the efficacy at 0.9 mg/kg/day with increased adverse events (AEs) documented (Summary of Clin. Pharm., p. 65).

The applicant reports that deflazacort treatment can inhibit or decrease the signs of inflammation based on in vitro and in vivo models; promoting functional gain, myogenic differentiation, myoblast fusion, and laminin expression in regenerating dystrophic muscle (Clinical Overview, pp. 23-24).

The applicant assessed the potential for deflazacort to adversely affect cardiac potassium ion channels through automated patch-clamp hERG channel assays. The applicant reports that 21-desDFZ and its primary metabolite, 6-β-OH-21-desDFZ demonstrated negligible inhibition at the highest concentration tested in the assay (10 µM); no IC50 values were calculable for either analyte.

4.5.3. Pharmacokinetics

The following text, based on the Clinical Overview, outlines the results of the applicant's pharmacokinetics studies listed in the table above.

Deflazacort absorbed following oral administration acts as a pro-drug that is converted by plasma esterases to the active 21-desDFZ metabolite. The elimination of this metabolite is primarily via the urine in rat, monkey, and human. The applicant reports that a typical fasted DMD patient of 41.3 kg would have an absorption/biotransformation half-time of 0.815 hours for deflazacort and a terminal elimination half-life of 2.4 hours (Study MP-104-NC-063). The Tmax of 21-desDFZ after oral administration of DFZ is 1-hour in rats, 1.5 to 2-hours in dogs and humans, and 2 to 4 hours in monkeys. The elimination half-life from plasma ranges 1.1 to 1.9 hours in healthy volunteers. The elimination half-life in children and adolescents with Duchenne muscular dystrophy (DMD) was 1.17 and 1.34 hours, respectively.

The fraction of 21-desDFZ bound to human plasma proteins in vitro was determined to be 40% bound over a range of concentrations from 0.31 to 6.33 µg/mL. In humans 21-desDFZ was found to be concentrated about 2-fold in red blood cells compared to whole plasma. Deflazacort metabolites were eliminated primarily via the urine in humans (65% of the administered dose over 24 hours) with the remainder not quantified, but assumed to be eliminated in the feces. There is no direct evidence of excretion of deflazacort, 21-desDFZ or 6-β-OH-21-desDFZ in human bile.

Data with healthy human subjects are consistent with linear oral dose proportionality of the active metabolite 21-desDFZ to oral dose of deflazacort. Mean Cmax averaged 10.4 ± 5.0, 19.8 ± 7.5, and 132.6 ± 52.5 ng/mL for the 3, 6, and 36 mg doses, respectively. Mean AUCinf averaged 38.5 ± 37.1, 64.9 ± 20.8, and 411.7 ± 148.5 ng.h/mL for the same 3 doses, respectively. For a 12-fold increase in dose, mean Cmax increased by a factor of 12.81, a roughly 1:1 increase. The regression of the relationship between 21-desDFZ Cmax and deflazacort dose exhibited linear PK (Clinical overview, pp. 17-18).

The applicant reports that in vitro CYP450 reaction phenotyping studies using recombinant human expressed CYP isoforms demonstrated that 21-desDFZ is a substrate for CYP3A4, but not

for other CYP isoforms (Study MP-104-NC-012). Drug-drug interactions would therefore be expected between deflazacort and other drugs that are either major inhibitors or major inducers of CYP3A4 metabolic activity. For example, warfarin (CYP3A4 inhibitor), itraconazole (CYP3A4 inhibitor), ketoconazole (CYP3A4 inhibitor), erythromycin (CYP3A4 inhibitor), and grapefruit juice (CYP3A4 inhibitor) will have effects when administered with deflazacort by increasing 21-desDFZ concentrations. The applicant recommends that concomitant use of deflazacort with moderate or strong CYP3A4 inhibitors and strong CYP3A4 inducers should be avoided. If concomitant use of a moderate or strong CYP3A4 inhibitor cannot be avoided, the applicant recommends that the dose of deflazacort should be reduced from 0.9 mg/kg/day to 0.3 mg/kg/day.

Study MP-104-CL-024 evaluated the PK parameters of deflazacort and 21-desDFZ in 8 subjects with end-stage renal disease (ESRD) on hemodialysis when compared to 8 healthy controlled subjects. Subjects with ESRD on hemodialysis exhibited a slightly reduced AUC exposure when compared to healthy controls (~ 90% of the AUC values in healthy controls). The applicant cites FDA guidance on PK in subjects with renal impairment (a 50% to 100% increase in AUC representing a substantial effect) in asserting that no adjustment in dose is needed in this subject population.

Study MP-104-CL-023 evaluated the PK parameters of deflazacort and 21-desDFZ in 8 subjects with moderate hepatic impairment when compared to 8 healthy matched controls. The applicant states that there were no clinically significant differences in AUC and Cmax between the hepatic impaired and healthy controlled subjects and therefore asserts that no dosing adjustment is needed in subjects with mild and moderate hepatic impairment.

This reviewer agrees with the applicant's recommendation that concomitant use of deflazacort with moderate or strong CYP3A4 inhibitors and strong CYP3A4 inducers should be avoided. Assessment of the applicant's recommendation that the deflazacort dose be reduced from 0.9 mg/kg/day to 0.3 mg/kg/day if concomitant use cannot be avoided is deferred to the clinical pharmacology reviewer. Analysis and discussion of the adequacy of the pharmacological studies and conclusions regarding dosing in renally or hepatically impaired individuals is also deferred to the clinical pharmacology reviewer.

4.6. Devices and Companion Diagnostic Issues

Not applicable. No companion device or diagnostic is included in the application.

4.7. Consumer Study Reviews

There are no label comprehension, patient self-selection, or other human factors studies

included with the submission.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies submitted to support the safety and efficacy of deflazacort are summarized in the table below. For a listing of all studies including pharmacokinetic and phase 1 studies, see Appendix 13.3.

Table 2. Listing of Clinical Trials for this NDA (See Appendix 13.3 for table of all studies). Source: Synopsis of Individual Studies, pp. 1-9

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
MP-104-NM-001	Phase 3, multicenter, double-blind, randomized, parallel-group, placebo controlled	Deflazacort 0.9 mg/kg/day, Deflazacort 1.2 mg/kg/day, Prednisone 0.75 mg/kg/day, or Placebo for the first 12 weeks of treatment. Deflazacort 0.9 mg/kg/day, Deflazacort 1.2 mg/kg/day, or Prednisone 0.75 mg/kg/day for the subsequent 40 weeks.	Assess the safety and efficacy of deflazacort and prednisone vs placebo at 12 weeks of treatment in improving muscle strength in D/B-MD patients	12 weeks placebo control followed by 40 weeks open label extension with all patients on Deflazacort or Prednisone.	196	DMD and BMD patients	9 Centers in 2 Countries (USA, Canada)
MP-104-NM-002	Phase 3, multicenter, double-blind,	Deflazacort 2 mg/kg once every 2 days, oral tablets	Asses the safety and efficacy of	Up to 2 years	29	Patients with DMD	5 centers in Italy.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	randomized, parallel-group, placebo controlled	Placebo once every 2 days, oral tablets.	deflazacort vs placebo in improving muscle function in patients with DMD				
MP-104-CL-022OLE	Phase 3, multicenter, open-label, extension study	Deflazacort 0.9 mg/kg qd, oral tablets	Assess the safety and tolerability of long-term use of deflazacort in DMD subjects who were previously enrolled in Study MP-104-CL-005.	Up to 16 months	1	Patients with DMD	5
Studies to Support Safety (Phase 1 studies listed in Appendix, Section 13.3)							
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
IND safety reports					8	Patients with DMD	

5.2. Review Strategy

As described by the applicant, the clinical development program for deflazacort consisted of 11 Phase 1 and Phase 3 studies conducted in healthy volunteers, subjects with moderate hepatic impairment, subjects with end stage renal disease (ESRD), and subjects with DMD. As of the 30-Oct-2015 cutoff date for the integrated safety database, 8 of the 11 studies were completed, 2 were ongoing, and 1 was not yet initiated. The entire clinical development program comprised 443 subjects (300 with DMD, 8 subjects from IND safety reports obtained from studies in other indications conducted by the prior sponsor, and 135 healthy volunteers, subjects with moderate hepatic impairment, and subjects with ESRD).

The focus of the review of efficacy and safety is on the two randomized, double-blind, placebo-controlled studies conducted in patients with DMD, studies MP-104-NM-001 and MP-104-NM-002, referred to also as studies NM-001 and NM-002, respectively. Both studies contribute to the safety analysis, including more than 2 years of follow-up for some patients in study NM-002. The different designs of the studies prevent pooling of efficacy results. The pivotal efficacy study is NM-001, which found statistically significant effects of deflazacort for primary and secondary endpoints as discussed in Section 7 of this review. Although some supportive evidence of efficacy may be found in the post-hoc analyses of secondary endpoints at 6 months and 1 year for study NM-002, the study failed to reach statistical significance for its primary endpoint at year 2, which was complicated by the departure from the study of most placebo patients.

The results of the applicant's analyses will initially be presented with reviewer commentary, followed by reviewer verification of key safety and efficacy claims. The clinical reviewer collaborated with the statistical reviewer to confirm the applicants' analyses. Please also refer to the separate statistical review.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study MP-104-NM-001: A double-blind, randomized safety and efficacy study of deflazacort in patients with Duchenne/Becker Muscular Dystrophy

6.1.1. Study Design

Study MP-104-NM-001 was a Phase 3, double-blind, randomized, multi-center study conducted from 1993-1995 to evaluate the safety and efficacy of deflazacort, evaluating the improvement

of muscle strength in boys with Duchenne (DMD) or Becker (BMD) muscular dystrophy aged 5 to 15 years.

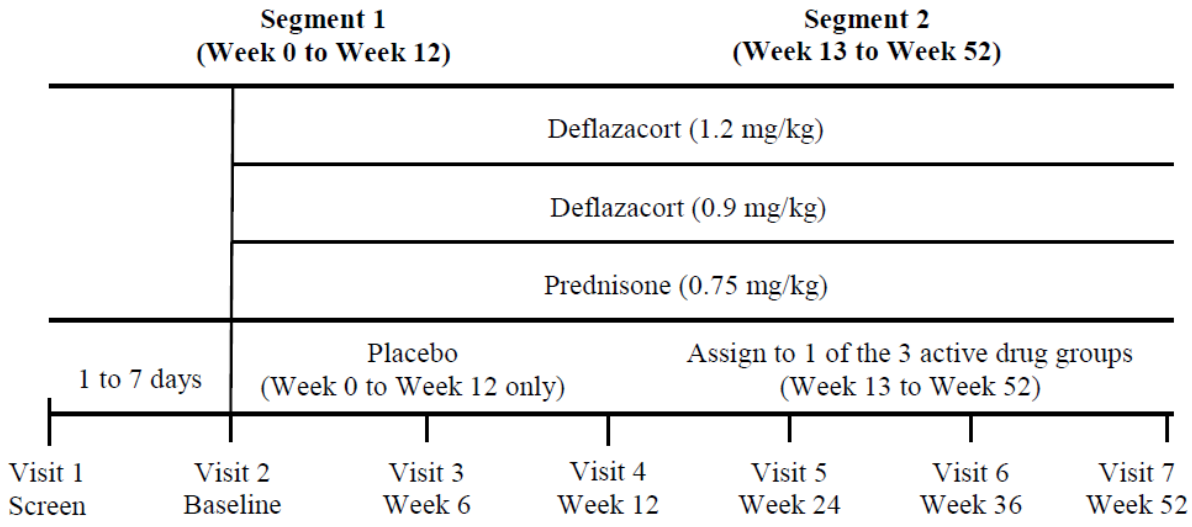
The study evaluated deflazacort and prednisone over a 52-week period, in 2 segments (see figure below). In Segment 1, deflazacort and prednisone were compared to placebo for the first 12 weeks of treatment. Patients who met all eligibility criteria were randomly assigned in a double-blind fashion to receive once-daily morning doses of 1 of the following treatments:

- Deflazacort 0.9 mg/kg/d (maximum daily dose of 72 mg)
- Deflazacort 1.2 mg/kg/d (maximum daily dose of 96 mg)
- Prednisone 0.75 mg/kg/d (maximum daily dose of 60 mg)
- Placebo tablets (number determined by patient's weight)

Following the initial 12-week segment, placebo patients were randomly assigned to 1 of the 3 active treatment groups for Segment 2 (the subsequent 40 weeks). Patients originally assigned to 1 of the 3 active treatment groups continued in that study arm for an additional 40 weeks in Segment 2.

Following Visit 7 (Week 52), or upon early termination, study medication was reduced by a maximum of 5 mg (prednisone equivalent) every 2 weeks until drug withdrawal was complete.

Figure 1: Design of study NM-001



Inclusion Criteria

Patients were males aged 5 through 15 years old with Duchenne or Becker muscular dystrophy. For inclusion into the study, patients were required to fulfill all of the following criteria:

1. The patient was male.
2. The patient was between the ages of 5 and 15 years old.
3. The patient had the onset of weakness before the age of 5 years old. If the boy had not been examined before the age of 5, documented history of the disease starting before that age was acceptable.
4. The patient must have had increased serum creatinine kinase activity at least 10 times the upper limit of normal at some stage in the illness prior to entry.
5. The patient had genetic analysis of the dystrophin gene. The complete mutation analysis must be demonstrated by the following specimen: DNA from blood cells or other tissue as evaluated by polymerase chain reaction or Southern Blot.
6. The patient demonstrated a clear alteration in dystrophin amount and/or distribution in the muscle. The dystrophin analysis was demonstrated by the following:
    a. Specimen: muscle biopsy
    b. Technology: immunostaining of muscle sections with 3 separate dystrophin antibodies, one against the N-Terminal and a second against C-Terminal portion of the molecule and a third one against the middle portion.
    − Duchenne muscular dystrophy - most would be negative with the 3 antibodies, some would show weak positive staining with the N-Terminal antibody.
    − Becker muscular dystrophy may be positive or "patchy" with all antibodies
    Note: Prior studies of genetic analysis and dystrophin characterization were acceptable. If no documentation, genetic testing and dystrophin analysis were performed prior to study entry. If 2 brothers participated in the study, genetic testing was required for only one of them.
7. Parent(s)/legal guardian(s) provided written informed consent for children <14 years of age; at 14 to 15 years of age, children signed with the parent(s)/legal guardian where applicable (i.e., as per provincial legislation).

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Prior long-term use of oral glucocorticoids (more than 1 year).
2. Active peptic ulcer disease or history of gastrointestinal bleeding or perforation.
3. Current cancer except non-metastatic basal cell or squamous cell carcinoma of the skin.
4. Organ transplant.
5. Prior or ongoing treatment with plasmapheresis or dialysis.
6. Any immunodeficiency disorder.

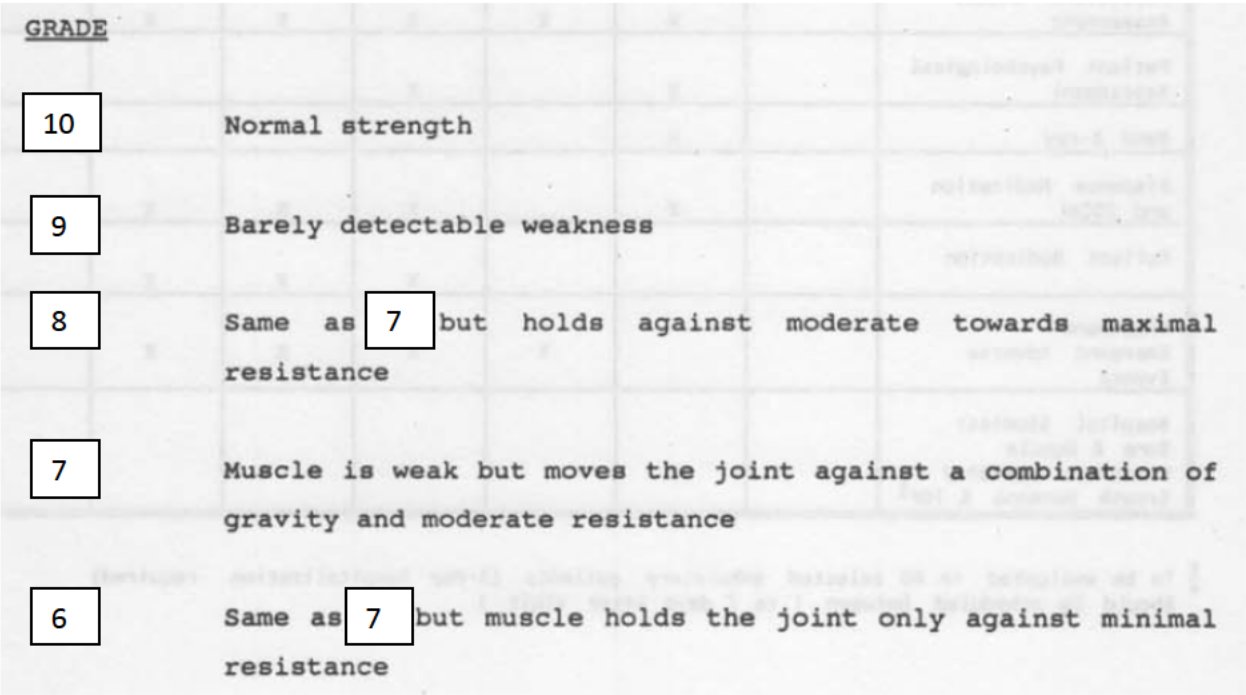
7. Any investigational drug use within 3 months of the baseline visit.
8. Hypersensitivity to deflazacort/prednisone.
9. Other intercurrent chronic illness that could interfere with clinical and laboratory indications of disease.
10. Any child who could not cooperate with the examiner.
11. Any use of oral steroids for ≥l month within 6 months of study entry
12. Any use of oral steroids for <1 month within 2 months of study entry
13. Normal muscle biopsy or muscle biopsy evidence of denervation, glycogen-storage disease.
14. Skin rash suggestive of dermatomyositis.
15. Patients with sensory abnormalities (exception: coincident mononeuropathy, such as a pressure palsy due to sitting in a wheelchair).
16. Clinical significant hepatic, neurologic, endocrine, renal or other major systemic findings that would make implementation/interpretation of the protocol's results difficult.
17. Previous fracture of vertebrae or hips within 1 month of study entry.
18. Current or recent infection with measles or chicken pox or contact with children with either disease.
19. Mental capacity limited to the extent that parent(s)/legal guardian/patient (when applicable) could not provide written informed consent or information regarding AEs or tolerance of study medication.
20. Any use of immunosuppressant within 90 days of study entry.
21. Immunization within 2 months of study entry.
22. The following medications are known or suspected to influence bone formation or resorption. Patients taking any of these medications were only enrolled in this study if they stopped them 30 days prior to entry:
    a. Calcitonin
    b. Fluorides
    c. Heparin
    d. Calcium-containing antacids
    e. Oral vitamin D preparations (>400 IU daily)
    f. Bisphosphonates
    g. Phenytoin and other anticonvulsants
    h. Calcium supplement (other than Os-Cal 250 provided by the sponsor)

Study Endpoints

The primary efficacy endpoint for this study was the change in average muscle strength score from baseline to week 12. Patients were asked to perform specific movements (see table below) in various positions (sitting, prone, side-lying, and supine) at each visit to evaluate the

change in severity of the disease over the course of the study. Each test was graded using an 11-point scale (from 10 = normal strength to 0 = no movement), as described in the following figure and table copied from the applicant.

Figure 2: Muscle strength grading. Source: NM-001 protocol, p. 55



GRADE	
10	Normal strength
9	Barely detectable weakness
8	Same as 7 but holds against moderate towards maximal resistance
7	Muscle is weak but moves the joint against a combination of gravity and moderate resistance
6	Same as 7 but muscle holds the joint only against minimal resistance

5	The muscle is capable of transient resistance but collapses abruptly. This degree of weakness is difficult to put into words, but it is a muscle which is able to move the joint against gravity and an additional small amount of resistance. It is <u>not</u> to be used for muscles capable of sustained resistance throughout the whole range of movement.
4	Muscle cannot move against resistance but moves the joint fully against gravity. With the exception of knee extensors, the joint must be moved through the full mechanical range against gravity. If a patient has contractures that limit movement of the joint, the mechanical range will obviously be to the point at which the contractures cause a significant resistance to the movement. In the case of the knee extensors "full range" will be considered to within 10° of full extension since it requires considerable strength to extend the knee fully.
3	Muscle moves the joint against gravity but not through the full extent of the mechanical range of the joint.
2	Muscle moves the joint when gravity is eliminated.
1	A flicker of movement is seen or felt in the muscle.
0	No movement.

Table 3: 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					

Secondary efficacy endpoints included the following:

- Change in average muscle strength score from Baseline or Week 12 to Week 52
- Change in myometric measurements (these measurements recorded muscle force in Newtons for shoulder abduction, elbow flexion/extension, and knee flexion/extension).
- Change in timed functional tests (standing from a lying position, climbing 4 stairs, running or walking for 30 feet, and propelling a wheelchair for 30 feet).

- Change in pulmonary function tests (forced vital capacity and maximum voluntary ventilation)
- Muscle metabolic markers (aspartate aminotransferase (AST), creatine kinase (CK) and lactate dehydrogenase (LDH))
- Physician global assessment using an analog scale (number line) where 0 cm = "no symptoms" and 10 cm = "as bad as it could be."

Of the secondary endpoints described above, the change from Week 12 to Week 52 for the average muscle strength score was the only assessment that was identified as a key secondary endpoint (i.e., controlled for Type I error).

Statistical Analysis Plan

The applicant describes the statistical analysis plan as follows for NM-001. *Note that not all analyses planned in the protocol could be completed due to records loss since the study was completed in the 1990s, as described in the protocol amendments section below. See the separate statistical review for further analysis of the applicant's statistical plan.*

"Two analysis populations were planned for this study:

- The Safety Population included all patients who receive at least 1 dose of study medication.
- The Intent-to-Treat (ITT) Population included all patients randomized into the study.

The efficacy analyses were conducted using the ITT Population.

All safety analyses were conducted using the Safety Population, except for the analysis statural growth, where the ITT Population was used.

For continuous variables, summary statistics including number of patients with data, mean, standard deviation (SD), median, minimum, and maximum were provided. For categorical variables, the number of patients and percentage for each category was presented. Least square (LS) Means or odds ratios as appropriate and 95% confidence intervals (CIs) were presented for statistical models as appropriate. Statistical testing was performed at the 0.05 level using 2-tailed tests. For efficacy analyses, the baseline value was defined as the mean of the assessments obtained from Visits 1 and 2 when both were present. If only one visit was present, the values from that visit were used as Baseline. For safety analyses, the baseline value was defined as the last available measurement collected before the date of Visit 2 (Week 0) when the first dose of study medication was administered.

Assessments occurring on the date of Week 0 were assumed to be taken prior to the first dose unless otherwise indicated. Change from Baseline was defined as the Value – Baseline. Demographic variables and baseline characteristics were summarized for the Safety Population overall and by treatment group. Demographic variables included age, gender, race, height, weight, and body mass index (BMI) collected at the Screening Visit. Baseline characteristics included average muscle strength, pulmonary function testing, timed functional testing, functional grading (leg and arm) and physician global assessment.

Efficacy Analysis

The primary efficacy endpoint was the change in average muscle strength score from Baseline to Week 12. The following null hypotheses were to be tested in a confirmatory sense at the 5% level of significance (2-sided test).

H0-1: There is no difference between deflazacort, prednisone and placebo with respect to change in average muscle strength score for patients treated up to 12 weeks.
H0-2: There is no difference between deflazacort and prednisone with respect to change in average muscle strength score from Week 12 to Week 52.

Other secondary efficacy endpoints and glucocorticoid-related safety outcomes were subjected to the same null hypotheses in a descriptive fashion. The other question of interest was to compare each of the deflazacort groups with prednisone with respect to change in average muscle strength score after 52 weeks of treatment from Baseline as well as with respect to all secondary endpoints. Patients randomized to the placebo group were evaluated in a descriptive fashion between 12 and 52 weeks of treatment after randomization to active medication.
The confirmatory main null hypothesis H0-1 was planned to be tested through an analysis of covariance model.

The main effects to be included into the model were:

- baseline average muscle strength score parameters (Visits 1 and 2)
- investigative site
- treatments (placebo; 0.75 mg/kg prednisone; 0.9 mg/kg or 1.2 mg/kg deflazacort)

The dependent variable was the change from Baseline (Visit 1 and 2, averaged) to Week 12.

The following contrasts were evaluated as primary outcome:

- Ll: placebo versus deflazacort (0.9 mg/kg)
- L2: placebo versus deflazacort (1.2 mg/kg)
- L3: placebo versus prednisone (0.75 mg/kg)

The overall significance level for each of these 2 contrasts was to be adjusted by the Dunnett technique. Secondary efficacy endpoints (see Section 9.5.3.2) were analyzed using the same

statistical techniques as described for the primary endpoint."
(NM-001 Body, pp. 44-45)

Protocol Amendments

The protocol for study NM-001 from December 18, 1992 was submitted with this application. There were no protocol amendments reported. The original statistical analysis plan needed to be amended as follows due to missing data.

Reviewer Comment: The following description of missing data is from the applicant's statistical analysis plan. Data regarding serious adverse events and laboratory values was available for the safety review in Section 8.

This study was conducted in the early 1990s. As responsibility for the study passed from the original sponsor to some of the study investigators and then to the current applicant, study materials such as completed case report forms and other data became unavailable or were not able to be obtained.

The following protocol planned analyses could not be performed because the data were not available:

- Medical history
- Physical examination
- Patient psychological assessment
- Bone and muscle metabolic markers
- Growth hormone and IGF
- Compliance and dose taken.
- Study termination (disposition)
- Serious AEs
- Laboratory data
- Concomitant medications

- Adverse events – no dates of study drug administration are available so all AEs were classed as treatment emergent. In the placebo group, the AEs were classed as treatment emergent to the second randomized treatment if the onset date was on or after the Visit 4 (Week 12) date.
- The analysis has been changed to an MMRM. This was not available at the time that the protocol was written but is a more appropriate analysis.
- The quantitative myometry testing data will be listed but will not be included in summary tables or statistical analyses due to the lack of a meaningful composite summary measure and questionable interpretation of results.

Data Quality and Integrity: Sponsor's Assurance

Reviewer comment: The applicant reports the following limitations of the available study data. Sufficient data are available for safety and efficacy assessments.

Study MP-104-NM-001 (formerly DE-MD-1192) (b) (4) IND safety reports from clinical studies being conducted with deflazacort around the world and spontaneous reports were submitted to this IND. Marathon was able to obtain copies of IND safety reports for deflazacort which included serious and unexpected AE data from 1 of the study sites. The AEs from these expedited reports were entered into the ISS database (Integrated Summary of Safety, p. 11).

Study MP-104-NM-001 was conducted in the late 1980s/early 1990s and as a result, not all data that may have been collected during that time are currently available. Several of the variables/domains that would normally be included in an integrated safety analysis are not included in the study databases. As a result, the ISS does not include the following evaluations:

- Concomitant medications
- Study completion/termination information

It is not possible to accurately differentiate between DMD and Becker muscular dystrophy (BMD) patients in study NM-001. There is no differentiation between DMD and BMD in the submitted data. The applicant estimates that <=5% of the patients in study NM-001 had BMD based on a subset of cases where BMD was identified. BMD is usually milder than DMD with a later age of onset. However, all patients in study NM-001 had the onset of muscular dystrophy symptoms before age 5 years.

Reviewer Comment: Although it is not possible to differentiate between DMD and BMD patients in study NM-001, the available records suggest that >=95% of the patients were DMD patients. It is therefore reasonable to interpret the results of study NM-001 as applying to DMD patients, although no clear effectiveness determination for BMD can be made.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant has provided attestation within the individual trial reports that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP) (NM-001 study report body, p. 15).

Financial Disclosure

Reviewer comment: The applicant has submitted the required financial disclosure information in section M1.3.4 of the application. The applicant makes the following statements regarding missing information.

"When Marathon licensed the exclusive US rights to these studies in 2014, multiple attempts were made to contact all of the investigators to obtain financial information with respect to (b) (4) Marathon (b) (4) for study MP-104-NM-001. Due to the amount of time that passed between when these studies were conducted and when Marathon licensed the rights, Marathon was either unable to make contact or solicit a response to the request for financial information for many of the investigators. A list of investigators for whom Marathon was able to obtain financial information from is provided [see table in Section 13.2].... All investigators have no disclosable financial interests (Financial Certification and Discosure, p. 3)."

Patient Disposition

The applicant provides the following information about the numbers of subjects randomized and the number who were available and used for the primary efficacy analysis.

Between 26 April 1993 (first patient) and 20 April 1995 (last patient last visit), a total of 196 patients were enrolled in the study. A summary of patient enrollment and study disposition for all patients is provided in the following table. All randomized patients were included in the ITT Population and in the Safety Population. Data regarding discontinuation or completion of the study for each patient could not be obtained. In an evaluation based on study visit dates, an estimated 156 patients completed the study (NM-001 body, p. 51).

Table 4: Study NM-001 Patient Disposition (Source: NM-001 Study Report Body, p. 163)

Patient Disposition
Randomized Patients

Status	Deflazacort 0.9 mg/kg/day N=51 n (%)	Deflazacort 1.2 mg/kg/day N=49 n (%)	Prednisone 0.75 mg/kg/day N=46 n (%)	Placebo N=50 n (%)	Total N=196 n (%)
Randomized Patients	51	49	46	50	196
Intent-to-treat Population [1]	51 (100.0%)	49 (100.0%)	46 (100.0%)	50 (100.0%)	196 (100.0%)
Safety Population [2]	51 (100.0%)	49 (100.0%)	46 (100.0%)	50 (100.0%)	196 (100.0%)
Entered Treatment Segment II	47 (92.2%)	47 (95.9%)	45 (97.8%)	50 (100.0%)	189 (96.4%)

Note: Percentages are based on the total number of patients who were randomized.
[1] Intent-to-treat (ITT) Population - All patients who were randomized and had at least 1 post-baseline assessment.
[2] Safety Population - All patients who took at least 1 dose of study medication.

Protocol Violations/Deviations

There were no major protocol violations or deviations resulting in the exclusion of a patient from Intent-to-treat or Safety analysis populations. Most of the deviations were related to missed pulmonary function assessments or out-of-window visits. Two patients had excessive weight gain [>25% of body weight or >10 kg in 3 months] as defined in the protocol, but may not have had the deflazacort dose reduced 50% as required in the protocol (NM-001 Study Report Body p. 52).

Table of Demographic Characteristics

Reviewer Comment: Note that there is generally no race/ethnic/gender-specific dosing for corticosteroids.

The Phase 3 placebo-controlled study NM-001 included only males because DMD is an x-linked recessive disease and female manifesting carriers are very rare. The study was largely limited to whites/Caucasians. The age range was limited to the pediatric population (ages 5-15 years). See the following figure from the applicant as well as the figure in Section 8.6 for the demographic characteristics of the analysis population.

Table 5: Demographic Characteristics of the Safety Population (Source: NM-001 Study Report Body, p. 54)

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)
Median	9.0	8.0	8.0	7.0	8.0
Min, Max	5, 15	5, 15	5, 15	5, 15	5, 15
Gender, n (%)					
Male	51 (100.0%)	49 (100.0%)	46 (100.0%)	50 (100.0%)	196 (100.0%)
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%)
Height (cm)					
N	51	49	46	50	196
Mean (SD)	131.47 (17.405)	130.00 (19.507)	131.01 (17.659)	129.65 (17.541)	130.53 (17.921)
Median	128.50	127.00	127.90	123.10	127.65
Min, Max	101.6, 180.0	97.0, 169.6	106.7, 170.0	101.3, 174.0	97.0, 180.0
Weight (kg)					
N	51	49	46	50	196
Mean (SD)	30.50 (13.171)	28.98 (11.238)	31.83 (15.458)	30.59 (15.339)	30.45 (13.814)
Median	26.40	25.50	25.40	23.20	24.65
Min, Max	17.1, 73.0	16.3, 69.5	15.5, 84.0	14.8, 95.0	14.8, 95.0
BMI (kg/m^2)[a]					
N	51	49	46	50	196
Mean (SD)	17.07 (3.893)	16.71 (2.999)	17.65 (4.173)	17.20 (3.644)	17.15 (3.683)
Median	16.18	16.69	16.19	15.89	16.24
Min, Max	9.8, 28.9	9.6, 25.5	12.1, 31.2	12.7, 31.4	9.6, 31.4

Abbreviations: BMI=body mass index; max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Notes: Age, gender, and race, were measured at the screening visit.
[a] BMI (kg/m^2) = weight (kg) / [height $(m)^2$]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As is characteristic of patients with DMD, all the patients in study NM-001 had elevated baseline creatine kinase levels, which is indicative of muscle damage due to the disease. Similar median baseline assessment values were obtained across study groups, as shown in the table below. There were some larger differences in means, attributed to outliers, as seen in the large range of baseline timed 30 foot running/walking for the deflazacort 0.9mg/kg group.

Table 6: 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

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
Timed-Functional Testing – Running or Walking 30 feet (seconds)					
n	35	36	34	37	142
Mean (SD)	28.90 (110.614)	9.65 (12.283)	12.79 (36.192)	7.18 (5.235)	14.50 (58.083)
Median	6.15	6.78	5.23	5.60	6.03
Min, Max	3.7, 658.8	3.5, 78.0	2.4, 216.2	2.9, 29.4	2.4, 658.8
Timed-Functional Testing – Propelling a Wheelchair 30 feet (seconds)					
n	10	10	10	9	39
Mean (SD)	19.72 (12.496)	23.88 (18.825)	31.59 (36.262)	20.14 (10.456)	23.93 (21.883)
Median	15.80	17.50	15.35	17.30	16.35
Min, Max	10.8, 52.8	9.5, 69.3	11.2, 130.8	8.5, 37.3	8.5, 130.8
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)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	1, 9	1, 10	1, 9	1, 9	1, 10
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)
Median	1.0	1.0	1.0	1.0	1.0
Min, Max	1, 5	1, 6	1, 5	1, 5	1, 6
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)
Median	10.50	9.50	9.25	9.55	9.50
Min, Max	4.5, 20.5	3.0, 19.5	3.0, 21.0	2.5, 21.5	2.5, 21.5

Reference: Table 14.1.3.1
Abbreviations: FVC=force vital capacity; max=maximum; min=minimum; MVV=maximum voluntary ventilation; n=number of observations; N=number of patients; SD=standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No meaningful analysis of treatment compliance and concomitant medication use is possible because these data are available for only 56 of 196 patients, due to the loss of 140 original case report forms (CRF) following completion of the protocol in 1995 (b) (4)

(b) (4). Review of the limited data available did not suggest a compliance difference among the study groups. Note that efficacy and safety data were transferred to an electronic database prior to the loss of the CRFs and were submitted by the applicant, but did not include the missing compliance and concomitant medication data.

Efficacy Results – Primary Endpoint

Study NM-001 yielded statistically significant results for the primary endpoint of muscle strength change for both deflazacort doses and the prednisone dose compared to placebo, as shown in the table below, copied from the applicant. Although these effects are statistically significant, they represent small changes on the eleven-point strength scale as illustrated in the following descriptive figures generated from the applicant's data. Although the changes are small over the course of the 12 week study, the slight decline in strength in the placebo group is visible in the figures below, as is the slight improvement in strength of both deflazacort groups.

Table 7: NM-001 Primary Endpoint Results (Source: NM-001 Body, p. 59)

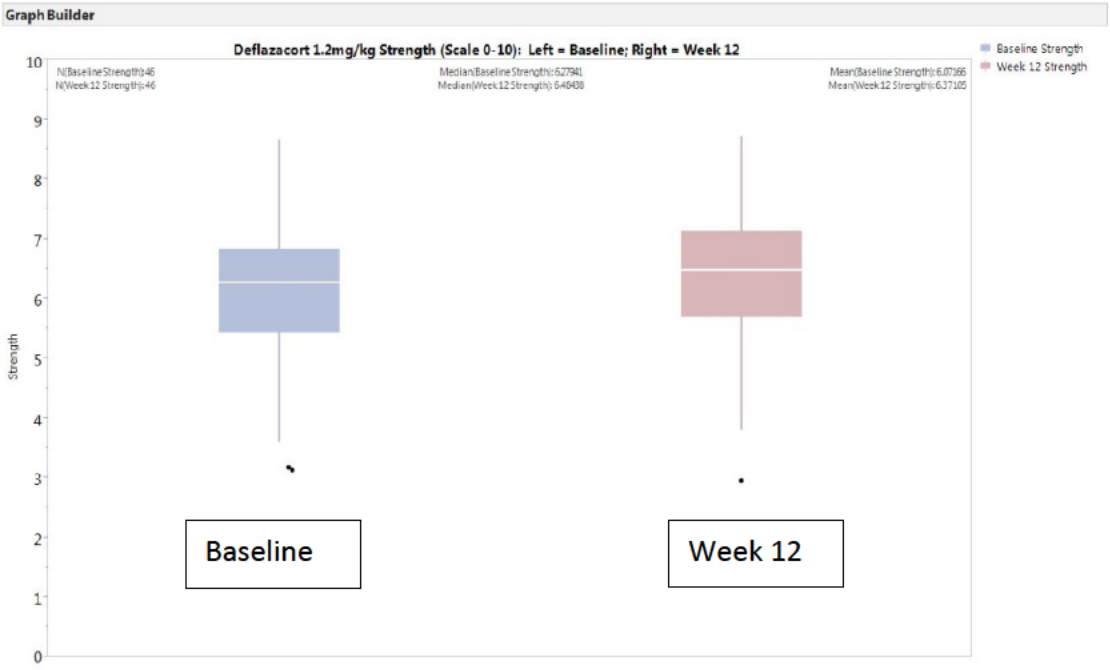
Visit	Treatment	N	n	Change from Strength Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Active - Placebo	95% CI	P-value
Week 12	Deflazacort 0.9 mg/kg/day	51	48	0.15 (0.01, 0.28)	0.25	(0.04, 0.46)	0.0173
	Deflazacort 1.2 mg/kg/day	49	46	0.26 (0.12, 0.40)	0.36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

Figure 3: Placebo Mean Strength (Scale 0-10): Left = Baseline; Right = Week 12

Figure 4: Deflazacort 0.9mg/kg Mean Strength (Scale 0-10): Left = Baseline; Right = Week 12

Figure 5: Deflazacort 1.2mg/kg Mean Strength (Scale 0-10): Left = Baseline; Right = Week 12



Reviewer Comment: Note that the primary endpoint effects listed in the table above, with a maximum change from baseline strength of 0.26 for deflazacort and -0.1 for placebo, are statistically significant but represent very small changes on the eleven-point strength scale. Over the course of only 12 weeks, such a small change would likely not be clinically meaningful for a patient. The muscle strength continues to improve beyond 12 weeks in the deflazacort group, as seen in the secondary endpoint 52-week analysis presented in Section 7.1.2, becoming more clinically meaningful.

Data Quality and Integrity – Reviewers' Assessment

As stated in Section 4.1, there was loss of case report forms and information matching subjects to study sites due to the age of the studies. It was therefore not possible to audit the case report forms or clinical source data.

Efficacy Results – Secondary and other relevant endpoints

The only key secondary endpoint that was statistically controlled for multiple comparisons was the following:

- The change in average muscle strength score from Week 12 to Week 52

The additional secondary endpoints that were evaluated during the trial were not statistically controlled for multiple comparisons. Therefore, these analyses are considered as exploratory and any positive results can only be viewed as nominally significant. The additional secondary endpoints evaluated in the trial include the following:

- The change in average muscle strength score from baseline to Week 52
- Pulmonary function testing
- Timed function testing
- Quantitative myometry
- Metabolic markers of muscle injury
- Functional grading
- Physician global assessment

Please see the previous section of this review that describes the nature and operationalization of these measures.

Unless otherwise stated, the sponsor has conducted the following analyses in relation to these endpoints:

- Change from baseline to Week 12 (the placebo-controlled portion of the trial)
- Change from Week 12 to Week 52 (comparing deflazacort to prednisone)
- Change from baseline to Week 52 (comparing deflazacort to prednisone)

Because the change from baseline to Week 52 is clinically more appropriate to evaluate when compared to the change from Week 12 to Week 52, the Week 12 to Week 52 results will not be presented in this review. The exception will be with respect to the key secondary endpoint which is statistically controlled for Type I error and is defined as the change in muscle strength from Week 12 to Week 52 and will therefore be considered below.

Muscle Strength Score

The only secondary endpoint that was statistically controlled for Type I error was the LS mean change from baseline in average muscle strength scores from Week 12 to Week 52 in the ITT population.

The following table, copied from the submission, presents the summary statistics of average muscle strength by visit:

Table 8: Summary Statistics of Average Muscle Strength Score by Visit to Week 52 (Intent-to-Treat Population). Source: NM-001 CSR, p. 63

	Original Randomized Treatment			Original Randomized Treatment + Re-Randomized Placebo Patients		
	Deflazacort 0.9 mg/kg/day N=51	Deflazacort 1.2 mg/kg/day N=49	Prednisone 0.75 mg/kg/day N=46	Deflazacort 0.9 mg/kg/day N=68	Deflazacort 1.2 mg/kg/day N=65	Prednisone 0.75 mg/kg/day N=63
Week 12 (n)	48	46	45	65	62	62
Mean (SD)	6.27 (1.540)	6.37 (1.328)	6.49 (1.636)	6.17 (1.541)	6.36 (1.347)	6.48 (1.579)
Median	6.19	6.48	6.71	6.03	6.40	6.68
Min, Max	2.3, 9.5	3.0, 8.7	2.6, 9.9	2.3, 9.5	3.0, 8.9	2.6, 9.9
Week 24 (n)	46	45	45	62	60	62
Mean (SD)	6.40 (1.667)	6.45 (1.369)	6.55 (1.711)	6.31 (1.655)	6.42 (1.382)	6.57 (1.639)
Median	6.00	6.53	6.94	5.97	6.43	6.94
Min, Max	2.8, 9.4	3.2, 9.0	2.3, 9.4	2.8, 9.4	3.2, 9.3	2.3, 9.4
Week 36 (n)	44	44	43	60	57	59
Mean (SD)	6.46 (1.696)	6.55 (1.404)	6.62 (1.857)	6.43 (1.624)	6.56 (1.405)	6.63 (1.754)
Median	6.26	6.60	7.00	6.25	6.62	6.94
Min, Max	2.4, 9.4	3.3, 9.0	1.6, 9.7	2.4, 9.4	3.3, 9.2	1.6, 9.7
Week 52 (n)	41	34	37	54	44	52
Mean (SD)	6.60 (1.685)	6.50 (1.589)	6.53 (1.841)	6.56 (1.683)	6.56 (1.575)	6.62 (1.777)
Median	6.76	6.65	7.00	6.60	6.65	6.99
Min, Max	3.7, 9.6	2.8, 9.1	1.6, 9.6	3.7, 9.6	2.8, 9.1	1.6, 9.6

Reference: Table 14.2.2.1.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.

The following table, copied from the submission, depicts the LS mean change in average muscle strength scores from Week 12 to Week 52 in the ITT population:

Table 9: Analysis of Change from Week 12 to Week 52 in Average Muscle Strength Score Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 62

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Week 12[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	41	0.17 (0.03, 0.31)	0.29	(0.08, 0.49)	0.0044
	Deflazacort 1.2 mg/kg/day	49	34	0.04 (-0.11, 0.19)	0.16	(-0.06, 0.37)	0.1788
	Prednisone 0.75 mg/kg/day	46	37	-0.12 (-0.26, 0.03)	-	-	-

Reference: Table 14.2.2.1.1
Abbreviations: CI=confidence interval; LS=least squares; n=number of observations; N=number of patients.
[a] Analysis results are from a mixed model of repeated measurements with a compound symmetry covariance structure. The model included treatment group, visit, treatment by visit, stratum, and site as fixed effects. The Week 12 value was included as a continuous covariate.
P-values and confidence limits are based on the Dunnett technique.

Reviewer's Comment: The preceding analyses were conducted using the Dunnett technique for control for multiple comparisons. The comparison between deflazacort 0.9 mg/kg/day and prednisone was statistically significant at p=0.004. The comparison between deflazacort 1.2 mg/kg/day and prednisone was not significant.

The following table, copied from the submission, depicts the LS mean change in average muscle strength scores from baseline to Week 52 in the ITT population:

Table 10: Analysis of Change from Baseline to Week 52 in Average Muscle Strength Score Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 65

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	41	0.39 (0.25, 0.54)	0.17	(-0.05, 0.38)	0.1649
	Deflazacort 1.2 mg/kg/day	49	34	0.38 (0.23, 0.54)	0.16	(-0.07, 0.38)	0.2136
	Prednisone 0.75 mg/kg/day	46	37	0.23 (0.07, 0.38)	-	-	-

Reference: Table 14.2.3.1
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 with a compound symmetry covariance structure. 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.

Reviewer's Comment: None of the results of the comparisons of deflazacort to prednisone from baseline to Week 52 were nominally significant (this analysis was not controlled for Type I error). Despite the statistical significance of the deflazacort 1.2 mg/kg/day versus prednisone comparison from Week 12 to Week 52, the current comparison from baseline generally appears more clinically relevant. However, it must be remembered that these comparisons are in relation to an active, albeit non-FDA approved, comparator. Therefore, any persistence of the observed benefit over placebo observed in average muscle strength testing at Week 12 cannot be determined because of the nature of the re-randomization of placebo subjects at Week 12 to one of the three active treatment arms.

Pulmonary Function Testing

The submission presents the results on the following PFTs that were evaluated during the trial:

- Forced vital capacity (FVC)
- Maximum voluntary ventilation (MVV)

Forced Vital Capacity

The following table, copied from the submission, depicts the LS mean change from baseline in FVC at Week 12 in the ITT population:

Table 11: Analysis of Change from Baseline at Week 12 in Forced Vital Capacity (L) Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 69

Visit	Treatment	N	n	Change from Baseline[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	45	0.145 (0.069, 0.222)	0.106	(-0.019, 0.231)	0.1185
	Deflazacort 1.2 mg/kg/day	49	44	0.119 (0.042, 0.197)	0.080	(-0.046, 0.205)	0.3117
	Prednisone 0.75 mg/kg/day	46	43	0.026 (-0.053, 0.105)	-0.014	(-0.140, 0.113)	0.9888
	Placebo	50	46	0.040 (-0.037, 0.116)	-	-	-

Reference: Table 14.2.2.3.1.1
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 following table, copied from the submission, depicts the LS mean change from baseline in FVC at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 12: Analysis of Change from Baseline at Week 52 in Forced Vital Capacity (L) Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 71

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	40	0.269 (0.189, 0.349)	-0.017	(-0.143, 0.108)	0.9357
	Deflazacort 1.2 mg/kg/day	49	31	0.202 (0.113, 0.291)	-0.084	(-0.216, 0.048)	0.2711
	Prednisone 0.75 mg/kg/day	46	37	0.286 (0.201, 0.370)			

Reference: Table 14.2.3.2
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.

Reviewer's Comment: There were no nominally significant results for any of the analyses of FVC.

Maximum Voluntary Ventilation

The following table, copied from the submission, depicts the LS mean change from baseline in MVV at Week 12 in the ITT population:

Table 13: Analysis of Change from Baseline at Week 12 in Maximum Voluntary Ventilation (L/min) Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 77

Visit	Treatment	N	N	Change from Baseline[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	45	3.796 (0.287, 7.306)	3.398	(-2.397, 9.192)	0.3743
	Deflazacort 1.2 mg/kg/day	49	44	5.693 (2.115, 9.271)	5.295	(-0.510, 11.100)	0.0830
	Prednisone 0.75 mg/kg/day	46	42	-0.071 (-3.764, 3.621)	-0.469	(-6.352, 5.413)	0.9954
	Placebo	50	46	0.398 (-3.127, 3.924)	-	-	-

Reference: Table 14.2.2.3.2.1
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 following table, copied from the submission, depicts the LS mean change from baseline in FVC at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 14: Analysis of Change from Baseline at Week 52 in Maximum Voluntary Ventilation (L/min) Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 79

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	39	7.859 (4.383, 11.336)	1.816	(-3.627, 7.258)	0.6795
	Deflazacort 1.2 mg/kg/day	49	32	9.621 (5.836, 13.406)	3.577	(-2.061, 9.216)	0.2721
	Prednisone 0.75 mg/kg/day	46	37	6.043 (2.383, 9.704)	-	-	-

Reference: Table 14.2.3.3
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.

Reviewer's Comment: There were no nominally significant results for any of the analyses of MVV.

Reviewer's Comment: The preceding PFT analyses failed to demonstrate any treatment benefit attributable to deflazacort. Given the disease stage of these subjects where pulmonary function is largely still intact, it is possible that a small treatment effect, even if present, would have been difficult to detect clinically.

Timed Function Testing

The submission presents the results on the following TFTs that were evaluated during the trial:

- Supine to standing
- 4 stair climb (4SC)
- Running/walking 30 feet
- Propelling a wheelchair 30 feet

Supine to Standing

The following table presents the summary statistics of the time (seconds) to stand from supine position by visit:

Table 15: Summary Statistics of Time (Seconds) to Stand from Supine Position by Visit to Week 52 (Intent-to-Treat Population). Source: NM-001 CSR, p. 81

	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
Baseline (n)	24	26	27	30
Mean (SD)	7.69 (4.998)	8.53 (5.534)	5.86 (2.845)	8.20 (4.570)
Median	6.40	6.38	5.40	7.10
Min, Max	2.5, 19.0	3.0, 26.3	1.7, 13.0	2.0, 24.5
P-value [a]	0.4120	0.8253	0.0261	-
P-value [b]	0.3743	0.0661	-	-
Week 6 (n)	23	24	28	29
Mean (SD)	6.67 (5.195)	6.58 (3.900)	5.94 (7.970)	9.04 (6.349)
Median	4.30	5.10	3.80	7.00
Min, Max	2.0, 19.0	1.8, 16.8	1.4, 45.4	1.7, 29.5
Week 12 (n)	24	23	28	28
Mean (SD)	7.12 (6.947)	5.80 (3.198)	6.14 (6.482)	10.04 (9.258)
Median	4.15	4.70	4.15	6.80
Min, Max	1.7, 33.0	1.9, 12.7	1.3, 31.9	1.8, 39.6
Week 24 (n)	23	24	27	----
Mean (SD)	5.86 (4.163)	5.55 (3.555)	5.72 (8.098)	----
Median	4.70	4.80	3.70	----
Min, Max	1.4, 19.5	2.3, 17.3	1.2, 45.3	----
Week 36 (n)	20	23	25	----
Mean (SD)	5.89 (4.752)	5.27 (3.175)	4.25 (2.180)	----
Median	4.00	4.20	3.60	----
Min, Max	1.3, 20.9	1.4, 13.0	1.1, 11.2	----
Week 52 (n)	20	15	23	----
Mean (SD)	6.18 (6.060)	5.05 (4.231)	4.04 (2.167)	----
Median	3.95	4.30	3.50	----
Min, Max	1.6, 28.7	1.7, 18.5	1.5, 10.2	----

Reference: Table 14.2.2.4.1.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.

Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

Reviewer's Comment: Subject's in the prednisone arm had a significantly faster time to stand at baseline compared to placebo and the deflazacort arms. This difference did not impact the analyses of this endpoint.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to stand from supine position at Week 12 in the ITT population:

Table 16: Analysis of Change from Baseline at Week 12 in Time (Seconds) to Stand from Supine Position Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 82

Time Point Statistic	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
Week 12				
n	23	23	26	28
Mean (SD)	-1.83 (2.125)	-2.78 (3.296)	-1.45 (1.452)	2.11 (6.385)
Median	-1.95	-1.65	-1.30	0.20
Min, Max	-6.2, 2.0	-13.9, 1.6	-5.4, 0.6	-3.5, 26.5
p-value [a]	0.0018	0.0002	0.0016	-
p-value [b]	0.4561	0.1395	-	-

Reference: Table 14.2.2.4.1.3
Abbreviations: max=maximum, min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

Reviewer's Comment: As outlined in the preceding table, the comparisons of both deflazacort groups to placebo were nominally statistically significant with low p-values at Week 12. There were no nominally significant results for the comparison between deflazacort and prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to stand from supine position at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 17: Analysis of Change from Baseline to Week 52 in Time (Seconds) to Stand from Supine Position Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 84

Time Point Statistic	Deflazacort 0.9 mg/kg/day N=51	Deflazacort 1.2 mg/kg/day N=49	Prednisone 0.75 mg/kg/day N=46
Week 52			
n	19	15	23
Mean (SD)	-2.53 (2.951)	-2.83 (2.739)	-1.53 (1.638)
Median	-1.50	-1.75	-1.35
Min, Max	-10.9, 0.4	-8.0, 1.5	-5.3, 2.4
p-value [a]	0.5898	0.2123	-

Reference: Table 14.2.2.4.1.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

Reviewer's Comment: There were no nominally significant results in the comparison of deflazacort to prednisone in the time (seconds) to stand from supine from baseline to Week 52.

4 Stair Climb
The following table presents the summary statistics of the 4SC by visit:

Table 18: Summary Statistics of Time (Seconds) to Climb 4 Standard Stairs by Visit to Week 52 (Intent-to-Treat Population). Source: NM-001 CSR, p. 86

	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
Baseline (n)	28	31	31	33
Mean (SD)	6.98 (6.684)	8.63 (8.916)	8.50 (14.109)	6.45 (4.847)
Median	4.90	5.90	4.30	5.25
Min, Max	1.7, 31.2	2.5, 48.3	1.0, 59.8	1.4, 24.3
P-value [a]	0.7241	0.4005	0.2018	-
P-value [b]	0.5663	0.0492	-	-
Week 6 (n)	27	30	32	34
Mean (SD)	6.77 (9.096)	7.89 (8.510)	6.43 (8.695)	7.86 (7.563)
Median	4.40	5.10	3.25	6.30
Min, Max	1.3, 48.9	1.7, 43.3	1.1, 43.1	1.2, 42.1
Week 12 (n)	27	29	30	33
Mean (SD)	4.61 (3.110)	6.77 (6.480)	5.03 (5.322)	7.59 (6.162)
Median	3.90	4.50	2.85	5.70
Min, Max	1.3, 12.9	1.6, 32.5	1.1, 20.8	1.4, 29.2
Week 24 (n)	27	31	30	----
Mean (SD)	7.07 (11.116)	6.38 (5.371)	5.28 (5.798)	----
Median	4.70	4.50	3.60	----
Min, Max	1.5, 60.0	1.2, 26.1	1.1, 22.5	----
Week 36 (n)	25	29	29	----
Mean (SD)	7.26 (10.927)	6.17 (6.854)	5.36 (6.880)	----
Median	4.20	4.00	3.10	----
Min, Max	1.0, 55.7	1.3, 35.8	1.1, 32.5	----
Week 52 (n)	22	20	27	----
Mean (SD)	4.30 (4.035)	6.08 (5.295)	6.09 (8.253)	----
Median	3.45	3.95	3.00	----
Min, Max	1.1, 19.7	1.4, 19.3	1.2, 31.8	----

Reference: Table 14.2.2.4.2.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value of zero were excluded from the analysis.

[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in 4SC at Week 12 in the ITT population:

Table 19: Analysis of Change from Baseline at Week 12 in Time (Seconds) to Climb 4 Standard Stairs Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 87

Time Point Statistic	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
Week 12				
n	27	28	29	33
Mean (SD)	-2.48 (4.075)	-2.99 (6.124)	-2.42 (6.837)	1.15 (1.788)
Median	-0.90	-1.48	-0.80	0.40
Min, Max	-18.3, 1.2	-32.3, 0.3	-37.4, 0.3	-1.7, 6.2
p-value [a]	<0.0001	<0.0001	<0.0001	-
p-value [b]	0.4687	0.2788	-	-

Reference: Table 14.2.2.4.2.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

Reviewer's Comment: As outlined in the preceding table, the comparisons of both deflazacort groups to placebo were nominally statistically significant with low p-values at Week 12. There were no nominally significant results for the comparison between deflazacort and prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in 4SC at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 20: Analysis of Change from Baseline to Week 52 in Time (Seconds) to Climb 4 Standard Stairs Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 89

Time Point Statistic	Deflazacort 0.9 mg/kg/day N=51	Deflazacort 1.2 mg/kg/day N=49	Prednisone 0.75 mg/kg/day N=46
Week 52			
n	22	20	26
Mean (SD)	-2.45 (3.092)	-3.79 (6.250)	-1.54 (5.856)
Median	-1.35	-1.73	-0.78
Min, Max	-11.5, 0.3	-29.0, -0.6	-28.7, 7.7
p-value [a]	0.0461	0.0012	-

Reference: Table 14.2.2.4.2.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank-sum test comparing deflazacort with prednisone.

Running/Walking 30 feet

The following table presents the summary statistics of the time (seconds) to run or walk 30 feet by visit:

Table 21: Summary Statistics of Time (Seconds) to Run or Walk 30 Feet by Visit (Intent-to-Treat Population). Source: NM-001 CSR, p. 91

	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
Baseline (n)	34	36	34	37
Mean (SD)	29.60 (112.198)	9.65 (12.283)	12.79 (36.192)	7.18 (5.235)
Median	6.30	6.78	5.23	5.60
Min, Max	3.7, 658.8	3.5, 78.0	2.4, 216.2	2.9, 29.4
P-value [a]	0.3369	0.0978	0.2729	-
P-value [b]	0.1225	0.0309	-	-
Week 6 (n)	33	31	35	37
Mean (SD)	17.66 (41.590)	7.15 (4.657)	7.64 (8.926)	27.94 (105.701)
Median	6.20	6.20	4.90	6.10
Min, Max	2.0, 227.6	3.6, 27.7	2.6, 51.0	3.2, 628.7
Week 12 (n)	34	32	33	37
Mean (SD)	14.13 (26.554)	7.04 (4.396)	6.70 (7.273)	16.06 (42.841)
Median	5.40	5.75	4.50	6.60
Min, Max	2.9, 121.5	3.3, 24.6	2.7, 43.6	3.3, 236.8
Week 24 (n)	32	31	32	----
Mean (SD)	13.11 (24.184)	6.19 (3.167)	6.94 (6.476)	----
Median	5.80	5.50	4.55	----
Min, Max	2.4, 112.6	2.8, 19.4	2.2, 33.7	----
Week 36 (n)	29	30	31	----
Mean (SD)	23.48 (64.784)	6.07 (3.143)	6.23 (5.922)	----
Median	5.40	5.10	4.30	----
Min, Max	2.9, 339.7	2.8, 19.0	2.4, 32.8	----
Week 52 (n)	27	22	28	----
Mean (SD)	18.32 (45.641)	6.32 (3.201)	9.01 (21.961)	----
Median	4.70	5.25	4.20	----
Min, Max	2.6, 227.7	3.0, 15.6	2.2, 120.5	----

Reference: Table 14.2.2.4.3.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements.
[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to run or walk 30 feet at Week 12 in the ITT population:

Table 22: Analysis of Change from Baseline at Week 12 in Time (Seconds) to Run or Walk 30 Feet Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 92

Time Point Statistic	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
Week 12				
n	33	32	33	36
Mean (SD)	-19.48 (106.421)	-2.84 (9.337)	-6.31 (29.910)	6.11 (34.523)
Median	-1.00	-1.10	-0.70	0.40
Min, Max	-611.8, 19.4	-53.4, 1.1	-172.6, 1.5	-1.9, 207.5
p-value [a]	<0.0001	<0.0001	<0.0001	-
p-value [b]	0.0656	0.1128	-	-

Reference: Table 14.2.2.4.3.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank-sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank-sum test comparing deflazacort with prednisone.

Reviewer's Comment: As outlined in the preceding table, the comparisons of both deflazacort groups to placebo were nominally statistically significant with low p-values at Week 12. There were no nominally significant results for the comparison between deflazacort and prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to run or walk 30 feet at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 23: Analysis of Change from Baseline to Week 52 in Time (Seconds) to Run or Walk 30 Feet Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 94

Time Point Statistic	Deflazacort 0.9 mg/kg/day N=51	Deflazacort 1.2 mg/kg/day N=49	Prednisone 0.75 mg/kg/day N=46
Week 52			
n	26	22	28
Mean (SD)	-24.62 (120.459)	-4.44 (13.094)	-4.22 (17.975)
Median	-1.10	-1.25	-0.75
Min, Max	-615.1, 8.7	-62.4, 0.0	-95.7, 1.5
p-value [a]	0.1853	0.0752	-

Reference: Table 14.2.2.4.3.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Nonambulatory patients were excluded from the analysis. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank-sum test comparing deflazacort with prednisone.

Reviewer's Comment: There were no nominally significant results for the comparison of deflazacort to prednisone in the time (seconds) to run or walk 30 feet at Week 52.

Propelling a Wheelchair 30 Feet

The following table presents the summary statistics of the time (seconds) to propel a wheelchair 30 feet by visit:

Table 24: Summary Statistics of Time (Seconds) to Propel a Wheelchair 30 Feet by Visit to Week 52 (Intent-to-Treat Population). Source: NM-001 CSR, p. 96

	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
Baseline (n)	10	10	10	9
Mean (SD)	19.72 (12.496)	23.88 (18.825)	31.59 (36.262)	20.14 (10.456)
Median	15.80	17.50	15.35	17.30
Min, Max	10.8, 52.8	9.5, 69.3	11.2, 130.8	8.5, 37.3
p-value [a]	0.9679	0.7783	0.6021	-
p-value [b]	0.5043	0.6822	-	-
Week 6 (n)	10	11	11	8
Mean (SD)	16.66 (11.476)	18.73 (14.148)	20.65 (14.230)	20.74 (11.230)
Median	12.10	15.20	14.20	17.15
Min, Max	9.5, 46.1	8.0, 58.4	7.5, 51.5	9.3, 44.3
Week 12 (n)	11	12	10	9
Mean (SD)	15.28 (7.104)	16.03 (7.792)	20.06 (11.350)	28.74 (24.152)
Median	13.00	14.80	14.40	17.50
Min, Max	8.5, 29.2	7.2, 31.8	7.2, 39.7	9.8, 84.1
Week 24 (n)	10	12	9	----
Mean (SD)	14.31 (5.528)	15.57 (8.527)	16.89 (7.027)	----
Median	12.75	13.10	15.50	----
Min, Max	9.1, 27.4	7.4, 34.2	10.0, 31.2	----
Week 36 (n)	9	11	9	----
Mean (SD)	14.70 (7.825)	20.95 (13.338)	16.61 (8.141)	----
Median	12.40	18.30	12.90	----
Min, Max	8.4, 34.0	8.2, 45.9	7.2, 29.8	----
Week 52 (n)	7	9	8	----
Mean (SD)	11.04 (3.157)	15.60 (11.152)	18.74 (15.319)	----
Median	9.30	10.00	11.65	----
Min, Max	8.2, 15.2	7.1, 36.8	7.2, 46.3	----

Reference: Table 14.2.2.4.4.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements.
[a] p-values are from a Wilcoxon rank sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to propel a wheelchair 30 feet at Week 12 in the ITT population:

Table 25: Analysis of Change from Baseline to Week 12 in Time (Seconds) to Propel a Wheelchair 30 Feet Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 97

Time Point Statistic	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
Week 12				
n	9	10	8	8
Mean (SD)	-3.84 (8.179)	-7.17 (11.899)	-13.46 (34.224)	1.33 (9.512)
Median	-1.05	-2.63	-2.05	2.10
Min, Max	-23.8, 3.4	-37.5, 1.6	-98.0, 3.7	-13.6, 17.9
p-value [a]	0.1820	0.0731	0.1486	-
p-value [b]	0.6367	0.6313	-	-

Reference: Table 14.2.2.4.4.3
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements. Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank-sum test comparing each treatment with placebo.
[b] p-values are from a Wilcoxon rank sum test comparing deflazacort with prednisone.

The following table, copied from the submission, depicts the LS mean change from baseline in time (seconds) to propel a wheelchair 30 feet at Week 52 between the deflazacort and prednisone arms in the ITT population:

Table 26: Analysis of Change from Week 12 to Week 52 in Time (Seconds) to Propel a Wheelchair 30 Feet Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 98

Time Point Statistic	Deflazacort 0.9 mg/kg/day N=51	Deflazacort 1.2 mg/kg/day N=49	Prednisone 0.75 mg/kg/day N=46
Week 52			
n	6	8	7
Mean (SD)	-4.18 (5.220)	-1.30 (6.146)	3.53 (9.137)
Median	-2.70	-0.20	0.00
Min, Max	-14.3, -0.1	-10.3, 5.8	-4.0, 22.5
p-value [a]	0.0774	0.4984	-

Reference: Table 14.2.2.4.4.6
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Observations with an analysis value or baseline value of zero were excluded from the analysis.
[a] p-values are from a Wilcoxon rank-sum test comparing deflazacort with prednisone.

Reviewer's Comment: There were no nominally significant results in any of the analyses of the time (seconds) to propel a wheelchair 30 feet.

Reviewer's Comment: As outlined in the preceding tables, nominally significant differences at low p-values at Week 12 for the comparison between deflazacort and placebo in the ITT population were observed for 3 of the 4 TFTS (time to stand from supine, 4SC, and time to run/walk 30 feet) evaluated during the trial. No differences were observed between deflazacort and prednisone at any timepoint. These results, while only nominally significant, may provide support for the clinical relevance of the small but statistically significant effect observed on the trial's primary muscle strength endpoint. The consistency of the findings in the placebo comparison at Week 12 argues for the plausibility of the observed effects representing a benefit attributable to deflazacort.

Quantitative Myometry Testing

Myometry measurements (shoulder abduction, elbow flexion/extension, and knee flexion/extension) were assessed during the trial. As described previously, the greatest of 3 measurements at each muscle group was recorded and an average was calculated for a patient at each visit across all 3 muscle measurements.

The submission states the following with respect to the myometry results at Week 12:

- Analysis of mean (SD) average percent changes from baseline to Week 12 showed a 38.16% (155.895) increase in muscle strength from baseline for the deflazacort 0.9 mg/kg/day group, a 17.49% (26.034) increase for the deflazacort 1.2 mg/kg/day group, a 12.60% (28.662) increase for the prednisone group, and a 5.83% (30.579) increase for the placebo group.

- When comparing each treatment with placebo by a Wilcoxon rank-sum test, the difference between the deflazacort 1.2 mg/kg/day group and the placebo group at Week 12 was found to be statistically significant (p = 0.0082, deflazacort 0.9 mg/kg/day versus placebo: p = 0.0599, prednisone versus placebo: p = 0.1632).

No nominally significant results were observed in the Week 12 to Week 52 analyses.

Reviewer's Comments: The verbatim statement above incorrectly states that the result for the comparison of deflazacort 1.2 mg/kg/day with placebo at Week 12 was "statistically significant." This result can only be considered as nominally significant given the lack of statistical control for Type I error. The lack of any other nominal findings for this endpoint greatly compromises any favorable conclusions that can be made based on this finding.

The submission also presents a number of further exploratory analyses that seek to correlate the myometry results with other endpoints. As the myometry result itself is exploratory, any positive results from these varied analyses lack statistical validity and are uninformative for the purposes of this review and will therefore not be discussed here.

Muscle metabolic markers (AST, CK, LDH)

AST, CK, and LDH decreased by week 6 for deflazacort 0.9 and 1.2 mg/kg compared to increased levels in the placebo group, as shown in the tables below copied from the applicant. *These descriptive results appear to indicate a reduction in metabolic markers of active muscle injury in the deflazacort and prednisone groups compared to the placebo group.*

Table 27: Summary Statistics of Creatine Kinase Results by Visit to Week 6 Safety Population. Source: NM-001 CSR, p. 671

Parameter Time Point [1] Statistic	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
Creatine Kinase (U/L)				
Baseline				
n	49	46	46	49
Mean (SD)	10263.9 (7209.85)	8039.1 (6141.21)	9860.8 (7423.64)	8686.1 (6299.59)
Median	9120.0	6335.0	9280.0	7080.0
Min, Max	1392, 29600	716, 27480	616, 44580	1280, 28900
Week 6				
n	48	43	46	47
Mean (SD)	6868.8 (5799.56)	5369.0 (3588.04)	6113.3 (5160.30)	9625.3 (6797.70)
Median	4805.0	5014.0	4800.0	9800.0
Min, Max	852, 23625	347, 14220	307, 25280	1304, 30100
Final Assessment				
n	48	43	46	47
Mean (SD)	6868.8 (5799.56)	5369.0 (3588.04)	6113.3 (5160.30)	9625.3 (6797.70)
Median	4805.0	5014.0	4800.0	9800.0
Min, Max	852, 23625	347, 14220	307, 25280	1304, 30100

[1] Final assessment is the last observed visit within the period.

Table 28: Summary Statistics of Lactate Dehydrogenase Results by Visit to Week 6 Safety Population. Source: NM-001 CSR, p. 657

Parameter Time Point [1] Statistic	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
Lactate Dehydrogenase (U/L)				
Baseline				
n	49	45	46	48
Mean (SD)	987.8 (565.84)	904.6 (467.64)	898.0 (420.17)	927.2 (452.40)
Median	901.0	910.0	916.5	915.0
Min, Max	320, 2960	285, 2700	180, 1924	227, 1960
Week 6				
n	48	44	45	47
Mean (SD)	773.1 (444.94)	708.2 (324.61)	700.5 (387.18)	1016.3 (640.45)
Median	737.5	698.0	663.0	955.0
Min, Max	215, 2360	214, 1311	159, 2020	220, 3030
Final Assessment				
n	48	44	45	47
Mean (SD)	773.1 (444.94)	708.2 (324.61)	700.5 (387.18)	1016.3 (640.45)
Median	737.5	698.0	663.0	955.0
Min, Max	215, 2360	214, 1311	159, 2020	220, 3030

[1] Final assessment is the last observed visit within the period.

Table 29: Summary Statistics of Aspartate Aminotransferase Results by Visit to Week 6 Safety Population. Source: NM-001 CSR, p. 644

Parameter Time Point [1] Statistic	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
Aspartate Aminotransferase (U/L)				
Baseline				
n	49	45	46	49
Mean (SD)	192.3 (115.29)	193.6 (120.71)	205.5 (126.67)	199.8 (131.32)
Median	174.0	158.0	187.0	178.0
Min, Max	39, 550	44, 680	28, 640	43, 512
Week 6				
n	48	44	46	47
Mean (SD)	163.1 (131.89)	142.5 (83.36)	156.9 (123.15)	214.3 (145.90)
Median	126.5	149.5	122.5	172.0
Min, Max	29, 632	27, 383	23, 580	47, 650
Final Assessment				
n	48	44	46	47
Mean (SD)	163.1 (131.89)	142.5 (83.36)	156.9 (123.15)	214.3 (145.90)
Median	126.5	149.5	122.5	172.0
Min, Max	29, 632	27, 383	23, 580	47, 650

[1] Final assessment is the last observed visit within the period.

Functional Grading

Functional grading was performed for both the arm and the leg.

Functional Leg Grading

The following table, copied from the submission, presents the summary statistics for the functional leg grading assessments by visit:

Table 30: Summary Statistics of Functional Leg Grading by Visit to Week 52 (Intent to- Treat Population). Source: NM-001 CSR, p. 100

	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
Baseline (n)	51	49	46	50
Mean (SD)	4.2 (3.37)	3.8 (3.09)	3.5 (3.28)	3.5 (3.10)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 9	1, 10	1, 9	1, 9
Week 6 (n)	48	47	46	50
Mean (SD)	4.1 (3.43)	3.9 (3.20)	3.4 (3.33)	3.7 (3.17)
Median	2.0	2.0	1.0	2.0
Min, Max	1, 9	1, 9	1, 9	1, 9
Week 12 (n)	48	47	45	50
Mean (SD)	4.0 (3.33)	3.9 (3.29)	3.7 (3.42)	3.8 (3.23)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 9	1, 9	1, 9	1, 9
Week 24 (n)	47	45	45	----
Mean (SD)	4.0 (3.35)	4.0 (3.35)	3.7 (3.49)	----
Median	2.0	2.0	2.0	----
Min, Max	1, 9	1, 9	1, 9	----
Week 36 (n)	43	44	42	----
Mean (SD)	4.1 (3.40)	3.8 (3.38)	3.5 (3.41)	----
Median	2.0	2.0	1.0	----
Min, Max	1, 9	1, 9	1, 9	----
Week 52 (n)	41	32	38	----
Mean (SD)	4.2 (3.57)	4.1 (3.43)	3.5 (3.50)	----
Median	2.0	2.0	1.0	----
Min, Max	1, 9	1, 9	1, 9	----

Reference: Table 14.2.2.5.1.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements.

The following table, copied from the submission, depicts the LS mean change from baseline in functional leg grading scores at Week 12 in the ITT population:

Table 31: Analysis of Change from Baseline at Week 12 in Functional Leg Grading Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 101

Visit	Treatment	N	n	Change from Baseline[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	-0.26 (-0.49, -0.03)	-0.32	(-0.65, 0.02)	0.0730
	Deflazacort 1.2 mg/kg/day	49	47	-0.23 (-0.47, 0.00)	-0.29	(-0.63, 0.05)	0.1138
	Prednisone 0.75 mg/kg/day	46	45	-0.10 (-0.34, 0.13)	-0.16	(-0.50, 0.18)	0.5675
	Placebo	50	50	0.06 (-0.17, 0.29)	-	-	-

Reference: Table 14.2.2.5.1.1
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 following table, copied from the submission, depicts the LS mean change from baseline in functional leg grading scores between the deflazacort and prednisone arms in the ITT population:

Table 32: Analysis of Change from Baseline at Week 52 in Functional Leg Grading Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 103

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	41	-0.13 (-0.38, 0.11)	-0.13	(-0.47, 0.21)	0.6194
	Deflazacort 1.2 mg/kg/day	49	32	0.12 (-0.14, 0.38)	0.13	(-0.22, 0.48)	0.6346
	Prednisone 0.75 mg/kg/day	46	38	-0.01 (-0.25, 0.24)	-	-	-

Reference: Table 14.2.3.8
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.

Reviewer's Comment: There were no nominally significant results for any of the analyses of functional leg grading scores.

Functional Arm Grading

The following table, copied from the submission, presents the summary statistics for the functional arm grading assessments by visit:

Table 33: Summary Statistics of Functional Arm Grading by Visit to Week 52 (Intent-to-Treat Population). Source: NM-001 CSR, p. 105

	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
Baseline (n)	51	49	46	50
Mean (SD)	1.9 (1.26)	1.9 (1.39)	1.7 (1.31)	1.9 (1.37)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 5	1, 6	1, 5	1, 5
Week 6 (n)	48	47	46	50
Mean (SD)	1.8 (1.21)	1.8 (1.38)	1.7 (1.26)	1.8 (1.39)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Week 12 (n)	48	47	45	50
Mean (SD)	1.8 (1.18)	1.8 (1.38)	1.7 (1.27)	2.0 (1.53)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Week 24 (n)	47	46	45	----
Mean (SD)	1.7 (1.17)	1.7 (1.30)	1.8 (1.38)	----
Median	1.0	1.0	1.0	----
Min, Max	1, 5	1, 5	1, 5	----
Week 36 (n)	43	44	42	----
Mean (SD)	1.9 (1.24)	1.8 (1.31)	1.8 (1.35)	----
Median	1.0	1.0	1.0	----
Min, Max	1, 5	1, 5	1, 5	----
Week 52 (n)	41	32	38	----
Mean (SD)	2.4 (0.95)	2.4 (1.07)	2.6 (1.11)	----
Median	2.0	2.0	2.0	----
Min, Max	1, 5	1, 5	1, 5	----

Reference: Table 14.2.2.5.2.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements.

The following table, copied from the submission, depicts the LS mean change from baseline in functional arm grading scores at Week 12 in the ITT population:

Table 34: Analysis of Change from Baseline at Week 12 in Functional Arm Grading Comparing Active Drug to Placebo (Intent-to-Treat Population). Source: NM-001 CSR, p. 106

Visit	Treatment	N	n	Change from Baseline[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	0.03 (-0.09, 0.16)	-0.10	(-0.30, 0.10)	0.4993
	Deflazacort 1.2 mg/kg/day	49	47	-0.10 (-0.24, 0.03)	-0.24	(-0.44, -0.04)	0.0156
	Prednisone 0.75 mg/kg/day	46	45	0.01 (-0.12, 0.14)	-0.13	(-0.33, 0.08)	0. 3427
	Placebo	50	50	0.14 (0.00, 0.27)	-	-	-

Reference: Table 14.2.2.5.2.1
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 following table, copied from the submission, depicts the LS mean change from baseline in functional arm grading scores between the deflazacort and prednisone arms in the ITT population:

Table 35: Analysis of Change from Baseline at Week 52 in Functional Arm Grading Comparing Deflazacort to Prednisone (Intent-to-Treat Population). Source: NM-001 CSR, p. 108

Visit	Treatment	N	n	Change from Baseline[a]	Between-treatment Difference in Change from Baseline[a]		
				LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Week 52	Deflazacort 0.9 mg/kg/day	51	41	0.61 (0.48, 0.74)	-0.20	(-0.39, 0.00)	0.0474
	Deflazacort 1.2 mg/kg/day	49	32	0.47 (0.33, 0.62)	-0.34	(-0.54, -0.13)	0.0006
	Prednisone 0.75 mg/kg/day	46	38	0.81 (0.67, 0.95)	-	-	-

Reference: Table 14.2.3.9
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.

Reviewer's Comment: As outlined in the preceding tables, nominally significant findings were observed in the comparison for deflazacort 1.2 mg/kg/day versus placebo at Week 12 in the ITT population and in the comparison of both deflazacort arms versus prednisone at Week 52. These groups were comparable at baseline, and the possible observation of a pattern of a dose-response relationship suggests that these findings may be plausible although the lack of statistical control precludes any definitive conclusions.

Physician Global Assessment

A physician global assessment was performed during the trial.

The following table, copied from the submission, presents the summary statistics for the physician global assessment by visit:

Table 36: Summary Statistics of Physician Global Assessment by Visit to Week 12 (Intent-to-Treat Population). Source: NM-001 CSR, p. 109

	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
Baseline (n)	51	49	46	50
Mean (SD)	10.99 (4.294)	10.17 (4.747)	9.61 (4.668)	10.22 (4.589)
Median	10.50	9.50	9.25	9.55
Min, Max	4.5, 20.5	3.0, 19.5	3.0, 21.0	2.5, 21.5
Week 6 (n)	49	48	46	48
Mean (SD)	11.38 (4.296)	9.99 (4.566)	9.84 (4.643)	10.38 (4.461)
Median	12.00	9.25	8.50	9.75
Min, Max	3.9, 19.5	2.5, 19.0	3.0, 20.0	3.5, 19.0
Week 12 (n)	47	45	44	50
Mean (SD)	10.97 (4.474)	10.59 (4.690)	9.82 (4.446)	10.76 (4.463)
Median	10.50	10.50	9.00	10.00
Min, Max	2.5, 19.5	4.0, 18.0	3.5, 21.0	5.0, 19.0

Reference: Table 14.2.2.6.2
Abbreviations: max=maximum; min=minimum; n=number of observations; N=number of patients; SD=standard deviation.
Note: Baseline was the average of Visit 1 and Visit 2 measurements.
P-values and confidence limits are based on the Dunnett technique.

The following table, copied from the submission, depicts the LS mean change from baseline for the physician global assessment at Week 12 in the ITT population:

Table 37: Analysis of Change from Baseline to Week 12 in Physician Global Assessment (Intent-to-Treat Population). Source: NM-001 CSR, p. 110

Visit	Treatment	N	n	Change from Baseline[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	47	0.70 (-0.08, 1.48)	-0.28	(-1.47, 0.91)	0.9008
	Deflazacort 1.2 mg/kg/day	49	45	0.79 (0.00, 1.59)	-0.19	(-1.39, 1.01)	0.9655
	Prednisone 0.75 mg/kg/day	46	44	0.40 (-0.39, 1.20)	-0.58	(-1.79, 0.63)	0.5319
	Placebo	50	50	0.98 (0.20, 1.75)	-	-	-

Reference: Table 14.2.2.6.1
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.

Reviewer's Comment: There were no nominally significant results for any of the analyses of the physician global assessment scores.

Durability of Response, Dose/Dose Response, Persistence of Effect

See Sections 7.1.4 and 7.1.5 for analysis and discussion.

6.2. Study MP-104-NM-002: Double-blind Study of the Efficacy and Safety of the Treatment of Duchenne Muscular Dystrophy (DMD) with a New Synthetic Corticosteroid: Deflazacort

6.2.1. Study Design

Overview and Objective

Study NM-002 was a Phase 3, double-blind, randomized, multicenter study conducted from 1988-1991 to evaluate the safety and efficacy of deflazacort in the improvement of muscle

strength in male patients with DMD having received deflazacort (2 mg/kg once every 2 days) or placebo (once every 2 days) in a 2:1 ratio (deflazacort:placebo). The study included 29 male patients suffering from DMD.

The primary objective was to assess the efficacy of deflazacort versus placebo in improving muscle function in patients with DMD from baseline to 2 years of treatment or loss of ambulation, whichever occurred first.

The major safety objective was to assess the corticosteroid-associated adverse event (AE) profile of deflazacort versus placebo, as well as to monitor treatment-emergent adverse events (TEAEs) and clinical laboratory data (Study synopsis, p. 1).

Inclusion Criteria
1) Male patients, able to walk, aged between 5 and 11 years;
2) symptoms onset before the age of 5;
3) diagnosis confirmed by: a) neurological exam; b) EMG; c) serum exams; d) muscle biopsy;
4) absence of absolute contraindications to the pharmaceutical product (glucose intolerance, relational and affective disorders, serious infectious diseases);
5) parents' informed consent.

No exclusion criteria were specified in the study protocol.

Study Endpoints

Study NM-002 defined the primary endpoint as the change in muscle strength from baseline to 2 years or loss of ambulation using a 0 to 5 point verbal rating scale, assessed manually, and converted to a Medical Research Council (MRC) index score. The MRC score, assessed at 6 months and at 1, 2, and 3 years, was expressed as a percentage of "normal strength" for the sum of 4 strength measurements (right triceps, right deltoid, right quadriceps, and right iliopsoas):

- Grade 5: muscle contracted normally against full resistance
- Grade 4: muscle strength was reduced but muscle contraction could still move joint against resistance
- Grade 3: muscle strength was further reduced such that the joint could be moved only against gravity with the examiner's resistance completely removed
- Grade 2: muscle could move only if the resistance of gravity was removed
- Grade 1: only a trace or flicker of movement was observed or felt in the muscle or fasciculations were observed in the muscle
- Grade 0: no movement was observed

In some instances, a + or – was added to the score to express an intermediate level of the scale and increase the precision of the evaluation. A + or – represents a value of 0.5.
The score was defined in the equation shown in the following figure taken from the applicant. Based on this equation, maximum strength was described as 100%, whereas minimum strength (no observable movement) was 0%.

Figure 6: Muscle strength score for study NM-002

$$\frac{Sum\ of\ muscle\ strength\ measurements}{(number\ of\ muscles\ tested)\ X\ 5} X\ 100\%$$

Secondary efficacy endpoints were assessed at 6 months and at 1, 2, and 3 years including:

- Change from Baseline in muscle function (walking, climbing stairs, standing up from a chair with no armrests, standing from sitting on floor [Gower's Maneuver], putting on a shirt without buttons)
- Change from Baseline in muscle strength using the Hammersmith myometer
- Time to loss of ambulation
- Age at time of loss of ambulation
- Condition as assessed by the patient's parent (improved, worsened, or stable)
- Cooperation as assessed by the patient's parent (good, sufficient, or nil)
- Physical therapy regularity (regular, sporadic, or none) as reported by patient's parent

Safety variables included:

- Adverse events (AEs)
- Side effects
- Statural growth (weight, height, and body mass index [BMI])
- Laboratory assessments

All safety variables were summarized descriptively by treatment group.

Statistical Analysis Plan

There was no statistical analysis plan in the original protocol. The applicant describes subsequent statistical analyses as follows for NM-002. Note that not all analyses for the protocol could be completed due to records loss since the study was completed in the 1980s-

1990s, as described in the protocol amendments section below. See the separate statistical review for further analysis of the applicant's statistical plan.

"Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed primarily using SAS® for Windows (version 9.3). All measured variables and derived parameters are listed individually and, if appropriate, tabulated by descriptive statistics. For continuous variables, summary statistics including the number of patients with data, mean, standard deviation (SD), median, minimum, and maximum are provided. For categorical variables, the number of patients and percentage for each category are presented. Least squares (LS) means or odds ratios, as appropriate, and 95% confidence intervals (CIs) are presented for statistical models, as appropriate. Statistical testing was performed at the 0.05 level using 2-tailed tests. (NM-002 Body, p. 29)"

Protocol Amendments

There were no protocol amendments reported by the applicant.

Data Quality and Integrity: Sponsor's Assurance

Since study NM-002 was conducted from 1988 to 1991, no imputation of missing data was possible. Very few laboratory and vital signs data were available. No data from the physical and eye examinations were available. There were two subjects for whom no CRFs or only pre-dose CRFs could be recovered; therefore those subjects were not included in the safety population.

Several of the variables/domains that would normally be included in an integrated safety analysis are not included in the study databases. As a result, the ISS does not include the following evaluations:

- Concomitant medications
- Vital signs for any group
- Study completion/termination information
- Laboratory results

For study NM-002, all of the information reported during the conduct of the study was not captured via a case report form (CRF). A 2-page blank source document that served as the CRF that captured subject and site information, visit date, muscle strength, muscle function, and weight was provided to all sites by the coordinating investigator. All other data were collected via physician progress notes (NM-002 study report body, p. 13).

Reviewer comment: Despite the above limitations of the NM-002 study data, sufficient data are available for safety and efficacy assessments when combined with the other available studies. Vital signs and laboratory data are available for study NM-001, but not for study NM-002.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant has provided attestation within the individual trial reports that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP) (NM-002 study report body, p. 13).

Financial Disclosure

Reviewer comment: The applicant has submitted the required financial disclosure information in section M1.3.4 of the application. For study NM-002, the principal investigator, Dr. Corrado Angelini, received licensing and consulting fees from the applicant years after completion of the study, so the quality of the study data could not have been biased by those payments at the time of the study. The applicant makes the following statements regarding missing information.

"When Marathon licensed the exclusive US rights to these studies in 2014, multiple attempts were made to contact all of the investigators to obtain financial information with respect to ... Marathon and Sanofi for study MP-104-NM-002. Due to the amount of time that passed between when these studies were conducted and when Marathon licensed the rights, Marathon was either unable to make contact or solicit a response to the request for financial information for many of the investigators. A list of investigators for whom Marathon was able to obtain financial information from is provided [see table in Section 13.2].... All investigators have no disclosable financial interests (Financial Certification and Discosure, p. 3)."

Patient Disposition

As described by the applicant, 31 patients were enrolled in the study. A total of 20 patients were randomized to treatment with deflazacort and 11 patients to treatment with placebo. Of the randomized patients, 18 patients were treated with deflazacort, and 11 patients were treated with placebo. Of these, 14 patients of the deflazacort group and 3 patients of the placebo group completed the study treatment period which was defined as study participation for at least 2 years following the first dose.

Table 38: Patient Disposition (Randomized Patients). Source: NM-002 Body, p. 33

	Deflazacort	Placebo	Total
	N = 20	N = 11	N = 31
Status	**n (%)**	**n (%)**	**n (%)**
Randomized patients	20	11	31
Safety population [1]	18 (90.0)	11 (100.0)	29 (93.5)
Completed the study period [2]	14 (70.0)	3 (27.3)	17 (54.8)

Source: Table 14.1.1
Abbreviation: N = total number of patients in each treatment group, n = number of patients who contributed to the analysis
Note: Percentages are based on the total number of patients who were randomized.
[1] Safety Population: All patients who took at least 1 dose of study medication with assessments beyond the baseline assessment. Due to the time that has elapsed since completion of the study, there were two subjects for which no CRFs or only pre-dose CRFs could be recovered; therefore those subjects are not included in the safety population.
[2] Completed the study treatment period was defined as study participation for at least 2 years following the first dose.

Protocol Violations/Deviations

No data on protocol violations or deviations were available.

Table of Demographic Characteristics

Reviewer Comment: Note that there is generally no race/ethnic/gender-specific dosing for corticosteroids.

The Phase 3 placebo-controlled study NM-002 included only males because DMD is an x-linked recessive disease and female manifesting carriers are very rare. The age range was limited to the pediatric population (ages 5-11 years).

No racial or ethnic demographics data were available for study MP-104-NM-002, which was conducted in Italy from 1988-1991. Patients were recruited in 5 centers in Italy from Padua, Bologna, Palermo, Bari and Pavia (12, 3, 5, 8 and 1 patients, respectively).

As seen in the following table copied from the applicant, the two treatment groups differed in the baseline mean value for Gower's Maneuver, which was slightly higher in the placebo group (16.20 seconds) than in the deflazacort group (11.89 seconds) as seen in the table above.

Reviewer Comment: The difference in Gower's Maneuver times might indicate a slightly worse baseline disease state in the placebo group that could complicate drug efficacy comparison. However, baseline mean strength measurements were similar between the two groups (deflazacort = 4.12; placebo = 4.14).

Table 39: Study NM-002 Demographic and Baseline Characteristics (Safety Population). Source: NM-002 Body, p. 34

Variable	Deflazacort	Placebo	Total
Status or Category	N = 18	N = 11	N = 29
Age [months]			
n	18	11	29
Mean (SD)	96.3 (14.36)	96.0 (16.03)	96.2 (14.73)
Median	94.0	91.0	93.0
Min, max	72, 120	68, 119	68, 120
Gender, n (%)			
Male	18 (100.0%)	11 (100.0%)	29 (100.0%)

Variable	Deflazacort	Placebo	Total
Status or Category	N = 18	N = 11	N = 29
Height [cm]			
n	18	11	29
Mean (SD)	121.63 (6.966)	122.14 (7.772)	121.82 (7.148)
Median	120.65	121.00	121.00
Min, max	107.5, 132.0	112.0, 138.0	107.5, 138.0
Weight [kg]			
n	18	11	29
Mean (SD)	25.27 (4.648)	24.92 (5.774)	25.13 (5.005)
Median	24.65	21.00	24.00
Min, max	17.5, 34.7	20.0, 35.0	17.5, 35.0
BMI [kg/m^2] [1]			
n	18	11	29
Mean (SD)	16.97 (1.966)	16.50 (2.348)	16.79 (2.091)
Median	16.95	15.60	16.50
Min, max	13.8, 21.2	14.3, 22.0	13.8, 22.0
Average muscle strength score			
n	18	11	29
Mean (SD)	4.118 (0.5696)	4.136 (0.6672)	4.125 (0.5967)
Median	4.313	4.375	4.375
Min, max	3.00, 5.00	3.00, 5.00	3.00, 5.00
Gower's Maneuver [seconds]			
n	18	10	29
Mean (SD)	11.89 (10.895)	16.20 (22.929)	13.43 (15.950)
Median	7.00	5.50	6.50
Min, max	4.0, 45.0	3.0, 75.0	3.0, 75.0
Gait			
n	18	11	29
Mean (SD)	2.6 (0.78)	2.5 (0.93)	2.6 (0.82)
Median	2.0	2.0	2.0

Abbreviations: BMI = body mass index, max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
[1] BMI [kg/m^2] = weight/height^2

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No other baseline characteristics are available.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No definition of treatment compliance was given in the protocol, and no data were collected. No restrictions on prior and concomitant therapy were described in the protocol, and no data were collected.

Efficacy Results - Primary Endpoint

Study NM-002 failed to yield statistically significant results for the primary endpoint (change in muscle strength from baseline to 2 years or loss of ambulation, whichever occurred first) at the pre-determined 2-year assessment time, with a between-treatment difference in change from baseline between the placebo and 2mg/kg alternating day deflazacort groups of 5.2 (95% CI [-3.16, 13.56], p = 0.2107).

As reported by the applicant, strength assessments performed following 6 months and 12 months did show nominally significant between-treatment differences in change from baseline strength between the placebo and 2mg/kg alternating day deflazacort groups of 6.97 (95% CI [1.24, 12.69], p = 0.0192) and 8.53 (95% CI [2.75, 14.32], p = 0.0056), respectively. The changes in strength after 6 and 12 months for the placebo and deflazacort groups are shown in the following figures generated from the applicant's data.

Reviewer Comment: Note that only 3 placebo patients remained in the study at the time of the 2-year assessment, making the primary endpoint results difficult to interpret. In the figures below using the 6 and 12 month data, when there were 10 and 9 placebo patients, respectively, there is a trend of small declines in mean strength in both the placebo and 2mg/kg alternating day groups, with greater declines in mean and minimum strength in the placebo group at 12 months.

Figure 7: Study NM-002 placebo group (N=11) strength at baseline, after 6 months, and after 12 months.

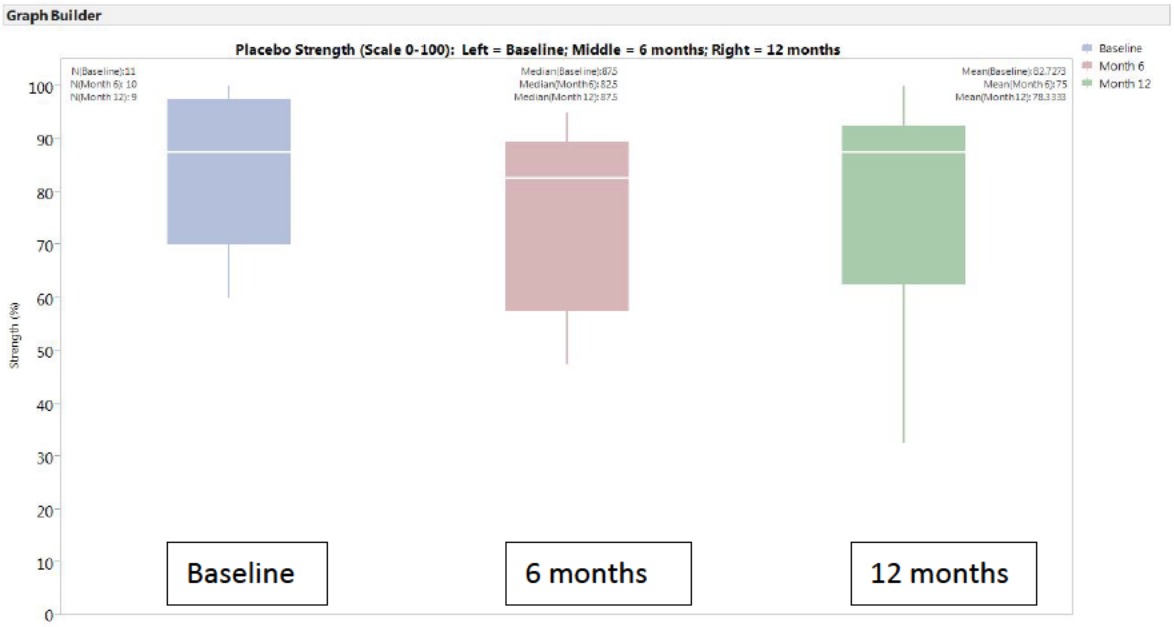


Figure 8: Study NM-002 deflazacort 2mg/kg alternating day group (N=18) strength at baseline, after 6 months, and after 12 months.

Data Quality and Integrity - Reviewers' Assessment

The applicant reports the several limitations of the available study data, described in Section 6.2.1. Sufficient data are available for efficacy and reported adverse event assessments, although vital sign and laboratory data are not adequate for clinically meaningful interpretation. Clinical site inspections were not possible due to the age of the clinical studies, with limited availability of original investigators and source documents.

Efficacy Results - Secondary and other relevant endpoints

For study NM-002, the following secondary efficacy endpoints were assessed at 6 months and at 1, 2, and 3 years. Because the submitted protocol does not contain information on the statistical analysis methods and because the key secondary efficacy endpoints were not pre-specified for this study, the following results are presented descriptively.

1. **Change from baseline in muscle function grade for walking**, ranging from normal = 1 to "confined to wheelchair" = 7.
   The results are shown in the following table, copied from the applicant. *The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, suggesting greater worsening in walking for the placebo group.*

Table 40: Summary Statistics of Change from Baseline in Muscle Function Grade for Walking (Safety Population). Source: NM-002 CSR, p. 42

Time Point	Deflazacort	Placebo
Statistics	N = 18	N = 11
Month 6, n	16	10
Mean (SD)	0.2 (0.66)	0.7 (0.95)
Median	0.0	0.5
Min, max	-1, 1	0, 3
Year 1, n	14	9
Mean (SD)	0.4 (0.50)	0.6 (0.53)
Median	0.0	1.0
Min, max	0, 1	0, 1
Year 2, n	12	3
Mean (SD)	0.7 (0.78)	1.3 (0.58)
Median	0.5	1.0
Min, max	0, 2	1, 2
Year 3, n	9	2
Mean (SD)	1.4 (1.59)	3.0 (1.41)
Median	1.0	3.0
Min, max	0, 5	2, 4

Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: 1 = normal, 2 = slightly anserine, lordotic and/or on tiptoes, 3 = moderately anserine, lordotic and/or on tiptoes, 4 = very anserine, lordotic and/or on tiptoes, 5 = only walks with support, 6 = can stand but cannot walk, 7 = confined to a wheelchair

2. **Change from baseline in timed 10 meter walk.**
   The results are shown in the following table, copied from the applicant. The time to perform the task is decreased relative to baseline through the year 1 assessment in the deflazacort group, whereas it increases consistently in the placebo group for all time-points. *This result suggests that deflazacort may improve timed walking for the first year, although it worsens thereafter, presumably due to disease progression.*

Table 41: Summary Statistics of Change from Baseline in Timed Muscle Function: Time to Walk 10 Meters [Seconds] (Safety Population). Source: NM-002 CSR, p. 43

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	13	8
Mean (SD)	-1.15 (1.994)	1.38 (1.685)
Median	-1.00	1.00
Min, max	-5.0, 1.0	0.0, 4.0
Year 1, n	12	8
Mean (SD)	-0.95 (2.036)	2.55 (3.625)
Median	-0.30	0.50
Min, max	-5.4, 1.0	-0.2, 9.0
Year 2, n	10	3
Mean (SD)	1.60 (4.812)	13.33 (22.234)
Median	0.00	1.00
Min, max	-3.0, 14.0	0.0, 39.0
Year 3, n	8	1
Mean (SD)	3.75 (5.898)	3.00 (----)
Median	3.00	3.00
Min, max	-2.0, 16.0	3.0, 3.0

Source data: Table 14.2.2.1.4
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: Patients unable to perform this test were excluded from the analysis.

3. **Change from baseline in muscle function grade for climbing stairs**, with worsening ability as the grading number increases to the inability to climb stairs at a grade of 7. The results are shown in the following table, copied from the applicant.
   The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, suggesting greater worsening in stair climbing for the placebo group.

Table 42: Summary Statistics of Change from Baseline in Muscle Function Grade: Stairs (Safety Population). Source: NM-002 CSR, p. 44

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	16	10
Mean (SD)	0.1 (0.62)	0.8 (0.79)
Median	0.0	1.0
Min, max	-1, 2	0, 2
Year 1, n	14	9
Mean (SD)	0.1 (1.10)	0.9 (0.78)
Median	0.0	1.0
Min, max	-2, 3	0, 2
Year 2, n	12	3
Mean (SD)	1.3 (1.42)	1.7 (1.53)
Median	1.0	2.0
Min, max	-1, 3	0, 3
Year 3, n	8	2
Mean (SD)	1.3 (1.75)	3.5 (3.54)
Median	1.0	3.5
Min, max	-1, 4	1, 6

Source data: Table 14.2.2.2.2
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: 1 = can handle stairs without help, 2 = places one hand on thigh, 3 = places both hands on thighs, 4 = goes up stairs erect but with help of the railing, 5 = goes up stairs with both hands on railing, 6 = hard time going up a few steps, 7 = unable to go up stairs

4. **Change from baseline in timed 4-stair climb**

   The results are shown in the following table, copied from the applicant. The time to perform the task is decreased relative to baseline at the 6 month assessment in the deflazacort group, whereas it increased in the placebo group at 6 months. From year 2 onwards, both the mean and median times for both groups are increased relative to baseline. *This result suggests that deflazacort may improve timed stair climbing initially, although it worsens later, presumably due to disease progression.*

Table 43: Summary Statistics of Change from Baseline in Timed Muscle Function: Time to go up 4 Stairs [Seconds] (Safety Population). Source: NM-002 CSR, p. 45

Time Point	Deflazacort	Placebo
Statistics	N = 18	N = 11
Month 6, n	15	8
Mean (SD)	-1.00 (2.952)	5.25 (9.721)
Median	-1.00	2.00
Min, max	-5.0, 7.0	-2.0, 28.0
Year 1, n	13	7
Mean (SD)	0.01 (8.758)	-1.17 (9.762)
Median	-1.00	1.60
Min, max	-12.8, 26.0	-22.8, 7.0
Year 2, n	9	2
Mean (SD)	4.00 (7.141)	2.00 (0.000)
Median	3.00	2.00
Min, max	-3.0, 19.0	2.0, 2.0
Year 3, n	5	1
Mean (SD)	2.80 (5.357)	7.00 (----)
Median	4.00	7.00
Min, max	-3.0, 10.0	7.0, 7.0

Source data: Table 14.2.2.2.4
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: Patients unable to perform this test were excluded from the analysis.

5. **Change from baseline in muscle function grade for standing up from chair**, with worsening ability as the grading number increases to the inability to stand up at a grade of 6. The results are shown in the following table, copied from the applicant.
   The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, *suggesting greater worsening in standing up from a chair for the placebo group.*

Table 44: Summary Statistics of Change from Baseline in Muscle Function Grade: Chair (Safety Population). Source: NM-002 CSR, p. 46

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	16	10
Mean (SD)	0.0 (0.89)	0.9 (0.74)
Median	0.0	1.0
Min, max	-2, 2	0, 2
Year 1, n	14	9
Mean (SD)	0.1 (1.03)	1.3 (1.12)
Median	0.0	2.0
Min, max	-2, 2	0, 3
Year 2, n	12	3
Mean (SD)	0.6 (1.08)	2.0 (1.00)
Median	0.0	2.0
Min, max	-1, 3	1, 3
Year 3, n	8	2
Mean (SD)	1.5 (1.41)	3.0 (0.00)
Median	1.0	3.0
Min, max	0, 4	3, 3

Source data: Table 14.2.2.3.2
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: 1 = normal, 2 = generally and/or with difficulty but without support, 3 = by placing one hand on the thigh or on the seat, 4 = using both hands for support, 5 = with other support, like nearby table, 6 = impossible

6. **Change from baseline in time to stand up from a chair with no armrests**
   The results are shown in the following table, copied from the applicant. The mean time to perform the task is decreased relative to baseline at the 1 year assessment in the deflazacort group, whereas it increased in the placebo group at 1 year. From year 2 onwards, the mean times for both groups are increased relative to baseline. *This result suggests that deflazacort may improve timed standing up initially, although it worsens later, presumably due to disease progression.*

Table 45: Summary Statistics of Change from Baseline in Timed Muscle Function: Time to Get Up from Chair [Seconds] (Safety Population). Source: NM-002 CSR, p. 47

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	14	8
Mean (SD)	0.34 (2.712)	1.31 (2.520)
Median	0.25	0.75
Min, max	-5.0, 6.0	-2.0, 6.0
Year 1, n	12	8
Mean (SD)	-0.27 (2.904)	4.04 (7.209)
Median	0.00	0.75
Min, max	-7.0, 5.0	-1.0, 16.3
Year 2, n	11	2
Mean (SD)	2.91 (3.653)	0.25 (1.061)
Median	1.00	0.25
Min, max	-0.5, 10.0	-0.5, 1.0
Year 3, n	5	1
Mean (SD)	1.30 (1.789)	1.50 (----)
Median	0.00	1.50
Min, max	0.0, 3.5	1.5, 1.5

Source data: Table 14.2.2.3.4
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: Patients unable to perform this test were excluded from the analysis.

7. **Change from baseline in muscle function grade for getting up from the floor (Gower's Maneuver)**, with worsening ability as the grading number increases to the inability to get up at a grade of 7. The results are shown in the following table, copied from the applicant.
   The mean changes are numerically larger in the placebo group at all time-points from month 6 onward. For the deflazacort group, there is no mean or median worsening of the functional grade until the year 2 assessment. *These results suggest greater worsening in standing up from the floor for the placebo group.*

Table 46: Summary Statistics of Change from Baseline in Muscle Function Grade: Gower's Maneuver (Safety Population). Source: NM-002 CSR, p. 48

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	16	10
Mean (SD)	-0.1 (0.77)	0.9 (0.88)
Median	0.0	1.0
Min, max	-2, 1	0, 3
Year 1, n	14	9
Mean (SD)	0.0 (0.68)	1.3 (1.12)
Median	0.0	1.0
Min, max	-2, 1	0, 4
Year 2, n	12	3
Mean (SD)	0.7 (0.65)	1.3 (0.58)
Median	1.0	1.0
Min, max	0, 2	1, 2
Year 3, n	8	2
Mean (SD)	1.4 (1.69)	3.0 (0.00)
Median	1.0	3.0
Min, max	0, 4	3, 3

Source data: Table 14.2.2.4.2
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: 1 = normal, 2 = raises the hips first by placing a hand on the floor, 3 = raises the hips first by placing both hands on the floor, 4 = places one hand on thigh, 5 = places both hands on thighs, 6 = only gets up with help of nearby objects, 7 = unable to get up

8. Change from baseline in time to stand up from sitting on the floor [Gower's Maneuver]

The results are shown in the following table, copied from the applicant. The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, *suggesting greater worsening in standing up from the floor for the placebo group.*

Table 47: Summary Statistics of Change from Baseline in Timed Muscle Function: Time to Perform Gower's Maneuver [Seconds] (Safety Population). Source: NM-002 CSR, p. 49

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	14	6
Mean (SD)	1.79 (10.319)	3.50 (4.324)
Median	-1.00	2.50
Min, max	-10.0, 32.0	0.0, 12.0
Year 1, n	10	6
Mean (SD)	0.96 (8.780)	1.62 (1.575)
Median	-1.10	2.00
Min, max	-5.0, 25.3	-0.3, 3.0
Year 2, n	8	2
Mean (SD)	0.38 (2.973)	4.50 (3.536)
Median	0.50	4.50
Min, max	-4.0, 4.0	2.0, 7.0
Year 3, n	4	1
Mean (SD)	0.75 (2.986)	5.00 (----)
Median	1.00	5.00
Min, max	-3.0, 4.0	5.0, 5.0

Source data: Table 14.2.2.4.4
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: Patients unable to perform this test were excluded from the analysis.

9. **Change from baseline in proximal upper limb muscle function**, with worsening ability as the grading number increases to the inability to raise the arms above the shoulders at a grade of 5. The results are shown in the following table, copied from the applicant.

   The mean changes are numerically larger in the placebo group at all time-points from month 6 onward. *These results suggest greater worsening in upper limb muscle function for the placebo group.*

Table 48: Summary Statistics of Change from Baseline in Muscle Function Grade: Upper Limbs (Safety Population). Source: NM-002 CSR, p. 50

Time Point	Deflazacort	Placebo
Statistics	**N = 18**	**N = 11**
Month 6, n	16	10
Mean (SD)	0.1 (0.50)	0.4 (0.84)
Median	0.0	0.0
Min, max	0, 2	0, 2
Year 1, n	14	9
Mean (SD)	-0.1 (0.27)	0.7 (1.41)
Median	0.0	0.0
Min, max	-1, 0	0, 4
Year 2, n	12	3
Mean (SD)	0.2 (0.58)	1.3 (2.31)
Median	0.0	0.0
Min, max	0, 2	0, 4
Year 3, n	8	2
Mean (SD)	0.5 (0.93)	1.0 (1.41)
Median	0.0	1.0
Min, max	0, 2	0, 2

Source data: Table 14.2.2.5.2
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: 1 = starting with the arms on hips, the patient can do a complete circle until arms are above head; is also able to raise a glass of water up to eye level, 2 = can move arms above the head, but cannot lift a weight, 3 = can bring forearms above the head, but must flex elbows or use other muscles, 4 = cannot raise arms above eyes, 5 = cannot raise arms above shoulders

10. Change from baseline in time to put on a shirt without buttons

The results are shown in the following table, copied from the applicant. The mean and median changes are consistently negative (meaning less time was needed to complete the task relative to baseline) in the deflazacort group at all time points, whereas the placebo group showed an increase in time needed for the task at years 1 and 2. *This result may suggest a beneficial effect from deflazacort. However, multiple patients in both groups were unable to complete the task, making interpretation of the result less clear.*

Table 49: Summary Statistics of Change from Baseline in Timed Muscle Function: Time to Put on a Shirt without Buttons [seconds] (Safety Population). Source: NM-002 CSR, p. 51

Time Point	Deflazacort	Placebo
Statistics	N = 18	N = 11
Month 6, n	7	3
Mean (SD)	-9.29 (10.626)	-5.33 (2.517)
Median	-9.00	-5.00
Min, max	-22.0, 7.0	-8.0, -3.0
Year 1, n	8	4
Mean (SD)	-11.09 (8.781)	4.85 (18.664)
Median	-14.50	2.00
Min, max	-20.6, 0.8	-14.6, 30.0
Year 2, n	6	2
Mean (SD)	-6.33 (11.759)	54.00 (93.338)
Median	-6.50	54.00
Min, max	-23.0, 7.0	-12.0, 120.0
Year 3, n	4	1
Mean (SD)	-6.00 (16.513)	-15.00 (----)
Median	-4.50	-15.00
Min, max	-24.0, 9.0	-15.0, -15.0

Source data: Table 14.2.2.5.4
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation
Note: Patients unable to perform this test were excluded from the analysis.

11. Change from baseline in muscle strength using the Hammersmith myometer

It appears that leg flexion and extension were assessed with the myometer based on the names of the parameters collected. *However, the precise placements of the myometer and the instructions given to study subjects were not defined in the study protocol, making interpretation of the results difficult.* A table of results is copied from the applicant below. *There is no clear pattern in the results.* At one year, the mean "Distance internal right malleolar patella" parameter is numerically greater in the placebo group, whereas the mean "Distance one-third of the patella" and "Weight one-third of the patella" parameters are numerically greater in the deflazacort group at one

year. *Beyond one year, interpretation is unclear due to the loss of most placebo patients from the study.*

Table 50: Summary Statistics of Change from Baseline of Hammersmith Myometer Muscle Strength (force measured in Newtons) (Safety Population). Source: NM-002 CSR, p. 52

Time Point	Deflazacort	Placebo
Statistics	N = 18	N = 11
Distance internal right malleolar patella		
Month 6, n	14	8
Mean (SD)	1.79 (1.051)	1.38 (1.061)
Median	2.00	1.50
Min, max	0.0, 3.0	0.0, 3.0
Year 1, n	14	7
Mean (SD)	1.82 (2.839)	2.14 (1.069)
Median	2.50	2.00
Min, max	-7.5, 4.0	1.0, 4.0
Year 2, n	11	3
Mean (SD)	1.14 (8.222)	4.00 (2.000)
Median	3.00	4.00
Min, max	-23.5, 5.0	2.0, 6.0
Year 3, n	8	2
Mean (SD)	4.13 (1.808)	4.00 (2.828)
Median	3.00	4.00
Min, max	3.0, 8.0	2.0, 6.0
Distance one-third of the patella		
Month 6, n	14	8
Mean (SD)	0.53 (0.466)	0.46 (0.504)
Median	0.55	0.35
Min, max	0.0, 1.0	0.0, 1.0
Year 1, n	13	7
Mean (SD)	0.93 (0.649)	0.79 (0.634)
Median	1.00	1.00
Min, max	0.0, 2.0	0.0, 1.8

Time Point	Deflazacort	Placebo
Statistics	N = 18	N = 11
Year 2, n	11	3
Mean (SD)	3.12 (5.948)	1.60 (0.529)
Median	1.40	1.80
Min, max	0.6, 21.0	1.0, 2.0
Year 3, n	8	2
Mean (SD)	1.41 (0.533)	1.50 (0.707)
Median	1.25	1.50
Min, max	1.0, 2.5	1.0, 2.0
Weight one-third of the patella		
Month 6		
n	14	8
Mean (SD)	1.07 (2.311)	0.51 (1.523)
Median	0.85	0.20
Min, max	-2.1, 6.3	-1.4, 2.7
Year 1, n	14	7
Mean (SD)	1.52 (2.239)	0.24 (1.330)
Median	0.85	0.10
Min, max	-2.1, 5.6	-1.5, 2.8
Year 2, n	11	3
Mean (SD)	1.45 (4.239)	-1.13 (0.603)
Median	1.90	-1.20
Min, max	-4.8, 8.0	-1.7, -0.5
Year 3, n	8	2
Mean (SD)	-0.58 (4.225)	-4.40 (2.546)
Median	-0.25	-4.40
Min, max	-6.7, 4.7	-6.2, -2.6

Source data: Table 14.2.2.6.2
Abbreviations: max = maximum, min = minimum, N = total number of patients in each treatment group, n = number of patients who contributed to the analysis, SD = standard deviation

12. Time to loss of ambulation from the start of the study

The applicant reports a difference in the time to loss of ambulation favoring the deflazacort group, as shown in the following table copied from the applicant. Review of the source documents provided with the application found that 1 patient in the deflazacort group lost ambulation within the 2 years of the primary efficacy assessment period of the study, compared to 3 patients in the placebo group. *This observation combined with the applicant's analysis appears to suggest that deflazacort may have a beneficial effect in delaying the loss of ambulation.*

Table 51: Kaplan-Meier Estimates of Time to Loss of Ambulation in Months from Start of Dosing Through End of Data Collection. Safety Population. Source: NM-002 CSR, p. 142

Statistic	Deflazacort N=18	Placebo N=11
n	18	11
n Censored (%)	12 (66.7%)	4 (36.4%)
Mean	58.0	31.0
25th Quartile	41.1	16.2
Median	63.0	31.9
75th Quartile	---	54.6
95% CI of Median	(35.1, NE)	(13.6, 54.6)
p-value [1]	0.0052	

Note: All estimates calculated using Kaplan-Meier product-limit survival curve methodology.
Note: NE = Not Estimable
[1] p-values from a log-rank test, comparing Deflazacort to placebo.

Table 52: Patients with narratives who lost ambulation during study NM-002 . Time after start of study is approximate. Due to lack of documentation, the applicant assigned the date of the first dose as 15 July 1988 for all study patients. Source: NM-002 CSR patient narratives, p. 219 and Discontinued patients, p. 16

Patient ID	Group	Time after start of study when ambulation lost
16	deflazacort	6 years & 1 month
21	deflazacort	3 years & 3 months
29	deflazacort	2 years & 11 months
39	deflazacort	1 year & 3 months
1	placebo	2 years & 9 months
5	placebo	4 years & 9

		months
6	placebo	4 months
13	placebo	1 year & 2 months
28	placebo	2 years & 5 months
38	placebo	1 year & 2 months
41	placebo	5 years
42	placebo	3 years

13. Age at the time of loss of ambulation

As shown in the figure below copied from the applicant, the mean and median ages at time of loss of ambulation were numerically greater for the deflazacort group compared with the placebo group, *suggesting that deflazacort may have a beneficial effect in delaying the loss of ambulation.*

Table 53: Summary Statistics of Age in Months at Time of Loss of Ambulation. Safety Population. Source: NM-002 CSR, p. 143

Statistic	Deflazacort N=18	Placebo N=11
n	6	7
Mean (SD)	148.1 (12.99)	126.3 (15.76)
Median	146.3	123.6
Min, Max	130, 163	104, 155

Note: Subjects who did not experience loss of ambulation within the duration of the study were excluded from this analysis.

14. Condition as assessed by the patient's parent (improved, worsened, or stable)

The results are shown in the following table copied from the applicant. At 6 months and 1 year a higher percentage of deflazacort-treated patients were assessed as improved or stable compared to placebo. A higher number of the placebo-treated patients were assessed as worsened at 6 and 12 months compared to those randomized to deflazacort. At 24 and 36 months, more deflazacort-treated patients were assessed as worsened compared to placebo, although the small number of remaining placebo patients (3 and 2, respectively) at those assessment times makes interpretation of results difficult. *These results appear to favor deflazacort over placebo up to 12 months. Note that this condition assessment is subjective and may be affected by unblinding due to the development of Cushingoid features in the deflazacort-treated patients.*

Table 54: Summary Statistics of Muscle Function - Patient Condition. Safety Population. Source: NM-002 CSR, p. 144

Time Point Status	Deflazacort N=18 n (%)	Placebo N=11 n (%)
Baseline		
Improved	0 (0.0%)	0 (0.0%)
Stable	10 (55.6%)	7 (63.6%)
Worsened	6 (33.3%)	1 (9.1%)
Month 6		
Improved	3 (16.7%)	0 (0.0%)
Stable	11 (61.1%)	6 (54.5%)
Worsened	2 (11.1%)	3 (27.3%)
Month 12		
Improved	2 (11.1%)	0 (0.0%)
Stable	10 (55.6%)	3 (27.3%)
Worsened	2 (11.1%)	4 (36.4%)
Month 24		
Improved	0 (0.0%)	0 (0.0%)
Stable	8 (44.4%)	3 (27.3%)
Worsened	4 (22.2%)	0 (0.0%)
Month 36		
Improved	1 (5.6%)	0 (0.0%)
Stable	4 (22.2%)	2 (18.2%)
Worsened	2 (11.1%)	0 (0.0%)

15. Cooperation as assessed by the patient's parent (good, sufficient, or nil)

As seen in the following table copied from the applicant, patient's cooperation was assessed as more likely to be "good" in the deflazacort-treated compared to placebo-treated patients at all time points. *Note that this assessment is subjective and may be affected by unblinding due to the development of Cushingoid features in the deflazacort-treated patients.*

Table 55: Summary Statistics of Muscle Function - Patient Cooperation. Safety Population. Source: NM-002 CSR, p. 145

Time Point Status	Deflazacort N=18 n (%)	Placebo N=11 n (%)
Baseline		
Good	12 (66.7%)	5 (45.5%)
Sufficient	5 (27.8%)	3 (27.3%)
Nil	0 (0.0%)	0 (0.0%)
Month 6		
Good	15 (83.3%)	5 (45.5%)
Sufficient	1 (5.6%)	3 (27.3%)
Nil	0 (0.0%)	1 (9.1%)
Month 12		
Good	13 (72.2%)	3 (27.3%)
Sufficient	1 (5.6%)	4 (36.4%)
Nil	0 (0.0%)	0 (0.0%)
Month 24		
Good	11 (61.1%)	2 (18.2%)
Sufficient	1 (5.6%)	0 (0.0%)
Nil	0 (0.0%)	1 (9.1%)
Month 36		
Good	7 (38.9%)	2 (18.2%)
Sufficient	0 (0.0%)	0 (0.0%)
Nil	0 (0.0%)	0 (0.0%)

16. Participation in physical therapy (regular, sporadic, or none).

As seen in the following table copied from the applicant, a numerically higher percentage of deflazacort-treated patients had participation in physical therapy assessed as "regular" at all time points compared to placebo-treated patients. *The meaning of this finding is unclear and could be interpreted as a beneficial effect from regular physical therapy leading to greater apparent efficacy in the deflazacort group, as greater ability to participate in physical therapy due to an effect of deflazacort, or as unblinding from the development of Cushingoid features that motivates deflazacort group patients to participate more in physical therapy.*

Table 56: Summary Statistics of Muscle Function – Physiotherapy. Safety Population. Source: NM-002 CSR, p. 146

Time Point Status	Deflazacort N=18 n (%)	Placebo N=11 n (%)
Baseline		
Regular	14 (77.8%)	7 (63.6%)
Sporadic	1 (5.6%)	0 (0.0%)
None	1 (5.6%)	1 (9.1%)
Month 6		
Regular	14 (77.8%)	6 (54.5%)
Sporadic	0 (0.0%)	1 (9.1%)
None	1 (5.6%)	2 (18.2%)
Month 12		
Regular	12 (66.7%)	6 (54.5%)
Sporadic	1 (5.6%)	0 (0.0%)
None	1 (5.6%)	1 (9.1%)
Month 24		
Regular	10 (55.6%)	2 (18.2%)
Sporadic	2 (11.1%)	0 (0.0%)
None	0 (0.0%)	1 (9.1%)
Month 36		
Regular	6 (33.3%)	2 (18.2%)
Sporadic	1 (5.6%)	0 (0.0%)
None	0 (0.0%)	0 (0.0%)

Durability of Response, Dose/Dose Response, Persistence of Effect

See Sections 7.1.4 and 7.1.5 for analysis and discussion.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Both the primary pivotal study (MP-104-NM-001) and the supportive study (MP-104-NM-002) had primary endpoints based on muscle strength. Study NM-001 used the change in average muscle strength score across 18 to 30 movements (described in Section 6.1.1) from Baseline to Week 12 as the primary efficacy endpoint. Patients were asked to perform specific muscle strength assessments in various positions (sitting, prone, side-lying, and supine) at each visit. Each test was graded using an 11-point scale (maximum strength of 10 to minimum strength of 0; based on the Medical Research Council (MRC) scale from 5 = normal strength; 5-, 4+, 4, 4-, 3+, 3, 3-, 2, 1, to 0 = no movement). Study NM-002 defined the primary endpoint as the change in muscle strength from Baseline to 2-years or loss of ambulation using a 0 to 5 point verbal rating scale converted to a Medical Research Council (MRC) index score expressed as a percentage of "normal strength" for the sum of 4 strength measurements (triceps, deltoid, quadriceps, iliopsoas). Note that study NM-001 allowed both ambulatory and non-ambulatory patients to have their strength assessed for the primary endpoint, whereas study NM-002 included only ambulatory patients for the primary endpoint calculation. Patients who lost ambulation during study NM-002 were dropped from the study.

Study NM-001 yielded statistically significant results for the primary endpoint (change in average muscle strength score from baseline to week 12), with a between-treatment difference in change from baseline mean muscle strength between the placebo and 0.9mg/kg deflazacort groups of 0.25 (95% CI [0.04, 0.46], p = 0.0173) at Week 12. For the placebo and 1.2mg/kg deflazacort groups, the between-treatment difference in change from baseline was 0.36 (95% CI [0.14, 0.57], p = 0.0003) at Week 12. Comparison between placebo and prednisone, considered part of non-FDA approved standard care for DMD, also yielded statistically significant results for the primary endpoint, with a between-treatment difference in change from baseline between the placebo and 0.75mg/kg prednisone group of 0.37 (95% CI [0.15, 0.59], p = 0.0002) at Week 12. *Note that these effects, for both deflazacort and prednisone, are statistically significant but represent very small changes (of less than one point) on the eleven-point strength scale. Over the course of only 12 weeks, such a small change would likely not be clinically meaningful for a patient. The muscle strength continues to improve beyond 12 weeks*

in the deflazacort group, as seen in the secondary endpoint 52-week analysis presented in Section 7.1.2 below, becoming more clinically meaningful.

Study NM-002 failed to yield statistically significant results for the primary endpoint at the pre-determined 2-year assessment time, with a between-treatment difference in change from baseline between the placebo and 2mg/kg alternating day deflazacort groups of 5.2 (95% CI [-3.16, 13.56], p = 0.2107). *However, this result is difficult to interpret because only 3 placebo patients remained in the study at the time of the 2-year assessment.* Strength assessments performed following 6 months and 12 months did show between-treatment differences in change from baseline between the placebo and 2mg/kg alternating day deflazacort groups of 6.97 (95% CI [1.24, 12.69], p = 0.0192) and 8.53 (95% CI [2.75, 14.32], p = 0.0056), respectively. Similar to the small effect size seen for study NM-001, the change in strength after 6 and 12 months was small for study NM-002 as seen in the figures generated from the applicant's data in Section 6.2.2. *They show a trend of small declines in mean strength in both the placebo (82.7% baseline to 78.3% at 12 months) and 2mg/kg deflazacort alternating day groups (82.4% baseline to 80.5% at 12 months). The deflazacort group has a numerically smaller decline (1.9% deflazacort vs. 4.4% placebo) of mean strength over the course of 12 months. These findings provide confirmatory evidence for the positive efficacy results of study NM-001.*

7.1.2. Secondary and Other Endpoints

The only key secondary endpoint that was statistically controlled for multiple comparisons was the change in average muscle strength score from Week 12 to Week 52 in study NM-001. The additional secondary endpoints that were evaluated during studies NM-001 and NM-002 were not statistically controlled for multiple comparisons. Therefore, these analyses are considered as exploratory and any positive results can only be viewed as nominally significant. *The loss of most placebo patients from study NM-002 at years 2 (8/11, 73% lost) and 3 (9/11, 82% lost) further complicates interpretation of results at years 2 and 3.* Please refer to the separate statistics review for detailed statistical analysis of study results.

The secondary endpoint results for NM-001, detailed in Section 6.1.2, are summarized here.

1. **Average muscle strength score from Week 12 to Week 52**, for the patients receiving active treatment throughout, showed a trend of continuing increases (deflazacort 0.9mg/kg: mean strength from 6.7 to 7.1; deflazacort 1.2mg/kg: mean strength from 6.4 to 6.5) for patients receiving either deflazacort dose throughout the duration of the study. *See the figures below, generated from the applicant's submitted data, for*

0.9mg/kg and 1.2mg/kg mean strengths at 12 and 52 weeks. For comparison of week 52 strength with baseline, see the figures in Section 7.1.4.

Figure 9: Mean Strength at weeks 12 and 52 in the deflazacort 0.9mg/kg group.

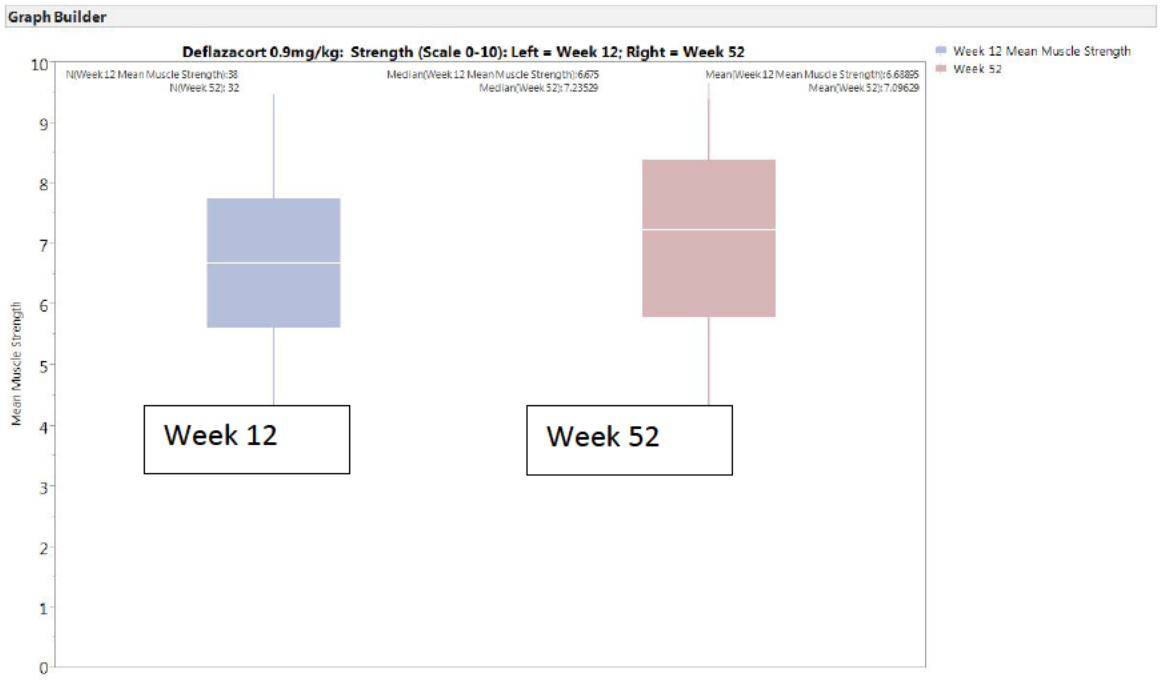
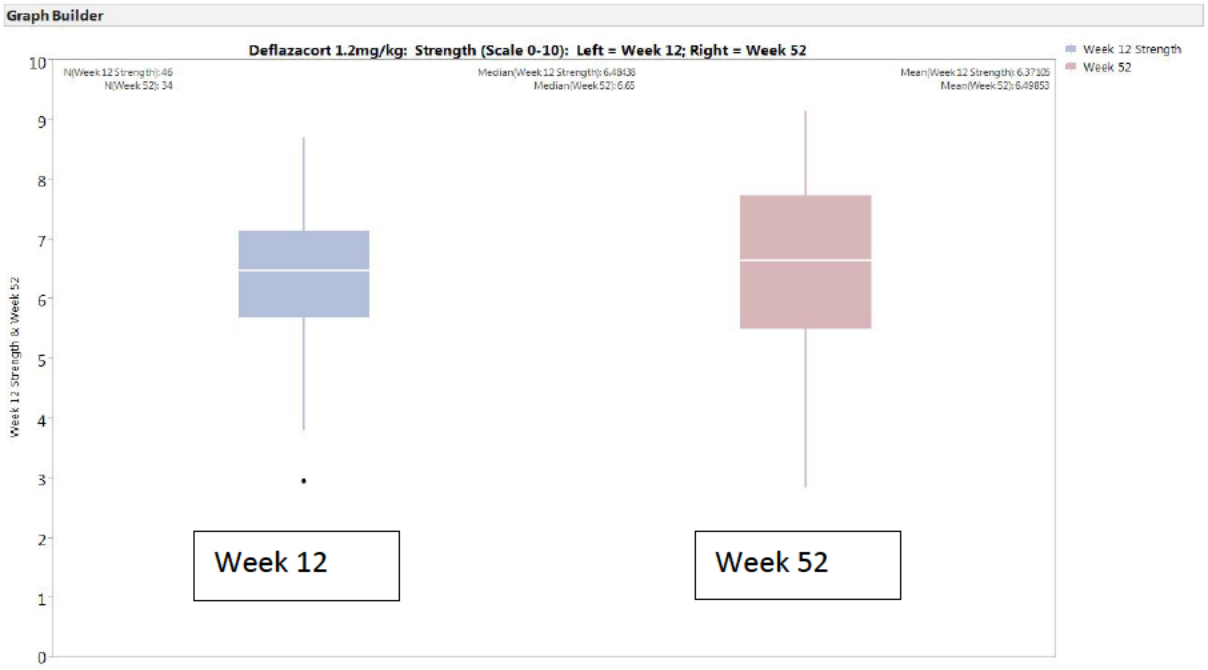


Figure 10: Mean Strength at weeks 12 and 52 in the deflazacort 1.2mg/kg group.



2. **Myometry measurements** (shoulder abduction, elbow flexion/extension, and knee flexion/extension)
   Analysis of mean (SD) average percent changes from baseline to Week 12 showed a 38.16% (155.895) increase in muscle strength from baseline for the deflazacort 0.9 mg/kg/day group, a 17.49% (26.034) increase for the deflazacort 1.2 mg/kg/day group, a 12.60% (28.662) increase for the prednisone group, and a 5.83% (30.579) increase for the placebo group. The difference between the deflazacort 1.2 mg/kg/day group and the placebo group at Week 12 was nominally significant (p = 0.0082).

3. **Timed functional tests**
   Supine to standing: Nominally significant reduction in time to standing (P = 0.0018, 0.0002 for deflazacort 0.9 and 1.2mg/kg versus placebo, respectively) at week 12.
   4 stair climb (4SC): Nominally significant reduction in time to climb 4 stairs (P < 0.0001 for both deflazacort 0.9 and 1.2mg/kg versus placebo) at week 12.
   Running/walking 30 feet: Nominally significant reduction in time to run or walk 30 feet (P < 0.0001 for both deflazacort 0.9 and 1.2mg/kg versus placebo) at week 12.

Propelling a wheelchair 30 feet: There were no nominally significant results in any of the analyses of the time (seconds) to propel a wheelchair 30 feet.

4. **Pulmonary function tests**: No nominally significant difference between deflazacort and prednisone in Forced Vital Capacity (FVC) or Maximum Voluntary Ventilation (MVV) at week 52 compared to baseline
5. **Muscle metabolic markers (AST, CK, LDH):** Decrease by week 6 for deflazacort 0.9 and 1.2 mg/kg and prednisone compared to increased levels in the placebo group.
6. **Functional grading for both the arm and the leg:** There were no nominally significant results for any of the analyses of functional leg grading scores. For functional arm grading, nominally significant findings were observed in the comparison for deflazacort 1.2 mg/kg/day versus placebo at Week 12 in the ITT population and in the comparison of both deflazacort arms versus prednisone at week 52. *The possible observation of a pattern of a dose-response relationship suggests that these findings may be plausible although the lack of statistical control at week 52 precludes any definitive conclusions.*
7. **Physician global assessment**: There were no nominally significant results for any of the analyses of the physician global assessment scores.

For study NM-002, the following secondary efficacy endpoints, detailed in Section 6.2.2 and summarized below, were assessed at 6 months and at 1, 2, and 3 years. Because the submitted protocol does not contain information on the statistical analysis methods and because the key secondary efficacy endpoints were not pre-specified for this study, the results are presented descriptively.

1. **Change from baseline in muscle function grade for walking**, ranging from normal = 1 to "confined to wheelchair" = 7. *The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, suggesting greater worsening in walking for the placebo group.*
2. **Change from baseline in timed 10 meter walk.**
   The time to perform the task is decreased relative to baseline through the year 1 assessment in the deflazacort group, whereas it increases consistently in the placebo group for all time-points. *This result suggests that deflazacort may improve timed walking for the first year, although it worsens thereafter, presumably due to disease progression.*
3. **Change from baseline in muscle function grade for climbing stairs**, with worsening ability as the grading number increases to the inability to climb stairs at a grade of 7. *The mean and median changes are numerically larger in the placebo group at all time-*

points from month 6 onward, suggesting greater worsening in stair climbing for the placebo group.

4. **Change from baseline in timed 4-stair climb**
   The time to perform the task is decreased relative to baseline at the 6 month assessment in the deflazacort group, whereas it increased in the placebo group at 6 months. From year 2 onwards, both the mean and median times for both groups are increased relative to baseline. *This result suggests that deflazacort may improve timed stair climbing initially, although it worsens later, presumably due to disease progression.*
5. **Change from baseline in muscle function grade for standing up from chair**, with worsening ability as the grading number increases to the inability to stand up at a grade of 6. The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, *suggesting greater worsening in standing up from a chair for the placebo group.*
6. **Change from baseline in time to stand up from a chair with no armrests**
   The mean time to perform the task is decreased relative to baseline at the 1 year assessment in the deflazacort group, whereas it increased in the placebo group at 1 year. From year 2 onwards, the mean times for both groups are increased relative to baseline. *This result suggests that deflazacort may improve timed standing up initially, although it worsens later, presumably due to disease progression.*
7. **Change from baseline in muscle function grade for getting up from the floor (Gower's Maneuver)**, with worsening ability as the grading number increases to the inability to get up at a grade of 7. The mean changes are numerically larger in the placebo group at all time-points from month 6 onward. For the deflazacort group, there is no mean or median worsening of the functional grade until the year 2 assessment. *These results suggest greater worsening in standing up from the floor for the placebo group.*
8. **Change from baseline in time to stand up from sitting on the floor [Gower's Maneuver]**
   The mean and median changes are numerically larger in the placebo group at all time-points from month 6 onward, *suggesting greater worsening in standing up from the floor for the placebo group.*
9. **Change from baseline in proximal upper limb muscle function**, with worsening ability as the grading number increases to the inability to raise the arms above the shoulders at a grade of 5.
   The mean changes are numerically larger in the placebo group at all time-points from month 6 onward. *These results suggest greater worsening in upper limb muscle function for the placebo group.*

10. Change from baseline in time to put on a shirt without buttons

The mean and median changes are consistently negative (meaning less time was needed to complete the task relative to baseline) in the deflazacort group at all time points, whereas the placebo group showed an increase in time needed for the task at years 1 and 2. *This result may suggest a beneficial effect from deflazacort. However, multiple patients in both groups were unable to complete the task, making interpretation of the result less clear.*

11. Change from baseline in muscle strength using the Hammersmith myometer

It appears that leg flexion and extension were assessed with the myometer based on the names of the parameters collected. *However, the precise placements of the myometer and the instructions given to study subjects were not defined in the study protocol, making interpretation of the results difficult. There is no clear pattern in the results.* At one year, the mean "Distance internal right malleolar patella" parameter is numerically greater in the placebo group, whereas the mean "Distance one-third of the patella" and "Weight one-third of the patella" parameters are numerically greater in the deflazacort group at one year. *Beyond one year, interpretation is unclear due to the loss of most placebo patients from the study.*

12. Time to loss of ambulation from the start of the study

The applicant reports a difference (mean 58 months for deflazacort 2mg/kg vs. 31 months for placebo) in the time to loss of ambulation favoring the deflazacort group. Review of the source documents provided with the application found that 1 patient in the deflazacort group lost ambulation within the 2 years of the primary efficacy assessment period of the study, compared to 3 patients in the placebo group. *This observation combined with the applicant's analysis appears to suggest that deflazacort may have a beneficial effect in delaying the loss of ambulation.*

13. Age at the time of loss of ambulation

The mean and median ages at time of loss of ambulation were numerically greater for the deflazacort (mean 148.1 months, median 146.3 months) group compared with the placebo group (mean 126.3 months, median 123.6 months), *suggesting that deflazacort may have a beneficial effect in delaying the loss of ambulation.*

14. Condition as assessed by the patient's parent (improved, worsened, or stable)

At 6 months and 1 year a higher percentage of deflazacort-treated patients were assessed as improved or stable compared to placebo. A higher number of the placebo-treated patients were assessed as worsened at 6 and 12 months compared to those randomized to deflazacort. At 24 and 36 months, more deflazacort-treated patients were assessed as worsened compared to placebo, although the small number of

remaining placebo patients (3 and 2, respectively) at those assessment times makes interpretation of results difficult. *These results appear to favor deflazacort over placebo up to 12 months. Note that this condition assessment is subjective and may be affected by unblinding due to the development of Cushingoid features in the deflazacort-treated patients.*

15. **Cooperation as assessed by the patient's parent (good, sufficient, or nil)**
    Patient's cooperation was assessed as more likely to be "good" in the deflazacort-treated compared to placebo-treated patients at all time points. *Note that this assessment is subjective and may be affected by unblinding due to the development of Cushingoid features in the deflazacort-treated patients.*
16. **Participation in physical therapy (regular, sporadic, or none).**
    A numerically higher percentage of deflazacort-treated patients had participation in physical therapy assessed as "regular" at all time points compared to placebo-treated patients. *The meaning of this finding is unclear and could be interpreted as a beneficial effect from regular physical therapy leading to greater apparent efficacy in the deflazacort group, as greater ability to participate in physical therapy due to an effect of deflazacort, or as unblinding from the development of Cushingoid features that motivates deflazacort group patients to participate more in physical therapy.*

Reviewer Comment:

The overall results of the secondary endpoints described above provide support for the clinical relevance of the small but statistically significant effect observed for the primary muscle strength endpoint of study NM-001. The consistency of the findings across studies NM-001 and NM-002 argues for the plausibility of the observed effects representing a benefit attributable to deflazacort.

7.1.3. Subpopulations

Subpopulation analysis by gender is not applicable because only males were included due to the nature of the disease. Analysis by race or ethnicity cannot be performed because those data were not collected in study MP-104-NM-002 and > 94% of patients were Caucasian in study MP-104-NM-001 (Summary of Clinical Efficacy, p. 68).

7.1.4. Dose and Dose-Response

As described by the applicant, the DMD patients pooled group includes 176 subjects who received at least 1 dose of deflazacort (93 subjects treated with 0.9 mg/kg/day, 65 subjects treated with 1.2 mg/kg/day, and 18 subjects treated with 2 mg/kg on alternate days) (Clinical Overview, p. 44).

For analysis and modeling of pharmacokinetics, please refer to the separate clinical pharmacology review.

As shown in the figures below, there was not a clinically significant difference in the change in mean strength over 52 weeks between the 0.9mg/kg and 1.2mg/kg deflazacort doses. Both doses showed a small increase of about half a point in the 11 point scale of mean strength over the course of the 52 week trial. This improvement compares favorably to the small decline in mean strength seen over 12 months in the 2mg/kg alternating day dose of study NM-002.

Figure 11: Deflazacort 1.2mg/kg group Mean Strength (Scale 0-10): Left = Baseline; Middle = Week 12; Right = Week 52.

Figure 12: Deflazacort 0.9 mg/kg group Mean Strength (Scale 0-10): Left = Baseline; Middle = Week 12; Right = Week 52.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

An improvement in strength testing was first seen at 12 weeks of treatment for the 0.9mg/kg and 1.2mg/kg deflazacort groups. Improvements in timed functional tests (time to standing, 4 stair climbing time) and serological markers of muscle injury (ALT, CK, LDH) were first seen at the 6 week assessments. See Sections 6.1.1 and 6.1.2 for details.

The duration of strength improvement for the 0.9mg/kg and 1.2mg/kg doses extended beyond the 12 week primary endpoint of study NM-001 and was still evident at the 52 week assessments, as shown in the figures in Section 7.1.4. For the 2mg/kg alternating day dose of study NM-002, the applicant reports a significant difference in the time to loss of ambulation favoring deflazacort: median 63.0 months for deflazacort; 31.9 months for placebo (P = 0.0052).

As seen in the adverse event tables for Study NM-002 in Section 8.4.5, there were more (8/11, ~73%) DMD patients in the placebo group of Study NM-002 who lost ambulation and were therefore discontinued from the study than in the deflazacort group (5/18, ~28%).

DMD is a progressive disease. Progressive muscle weakening would be expected after discontinuation of deflazacort treatment, although there were no specific assessments of the persistence of clinical benefit after the treatment was stopped in the applicant's studies. The therapeutic effects of deflazacort treatment would likely decline over time because of tolerability issues (subjects who experience adverse events and discontinue treatment). In published studies of deflazacort with a 0.9mg/kg daily starting dose, the dose had been decreased to 0.55 ± 0.09 mg/kg/day within about 7 years of starting the medication due to weight gain or other side effects (Matthews et al., 2016)

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

7.3. Integrated Assessment of Effectiveness

The Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness if FDA determines that such data and evidence are sufficient to establish effectiveness (Section 115(a) of the Modernization Act).

Study NM-001 was an adequate and well-controlled clinical investigation which showed that mean strength increased slightly (~2-3%) in both the 0.9 and 1.2 mg/kg/day deflazacort groups compared to a small (<1%) decrease in strength over the 12 week placebo arm of the study. There was a statistically significant difference in the 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: $p = 0.0003$) compared to placebo. For both deflazacort doses, the mean muscle strength continued to trend upwards beyond the 12-week placebo-control period to study completion at 52 weeks, at which time there was an approximate 5% improvement in mean strength compared to baseline (4% for the 1.2mg/kg dose and 6% for the 0.9mg/kg dose).

Although study NM-002 had a negative finding for the primary endpoint at year 2, the loss of

most placebo patients from the study at year 2 makes the primary endpoint result unclear. Positive results at year 1 combined with the results of the secondary endpoint analyses provide confirmatory evidence to support the results of study NM-001. In study NM-002, the deflazacort 2mg/kg alternating day dose had an approximate 2% drop in mean strength over 12 months compared to an approximate 4% decrease in mean strength in the 12 month placebo arm. Timed functional tests also supported the efficacy of deflazacort with reductions in time to standing, 4 stair climbing time, and 30 ft. walk time. Decreases in metabolic markers of muscle injury were also supportive of a benefit from deflazacort, with decreases in ALT, CK, and LDH by week 6 of treatment with deflazacort compared to increased levels in the placebo group. There is also an interesting finding from study NM-002 that 8/11 (~73%) of DMD patients in the placebo group lost ambulation compared to 5/18 (28%) in the deflazacort group, suggesting that deflazacort might help maintain ambulation in DMD patients. The mean and median ages at the time of loss of ambulation were more than 20 months later for the deflazacort group compared with the placebo group, providing further evidence that deflazacort may have a beneficial effect in delaying the loss of ambulation. Note that this finding is consistent with reports in the literature that deflazacort may delay the age at loss of ambulation by 1.4–2.5 years (Gloss et al., 2016). Taken together, these results support the conclusion that deflazacort can provide a meaningful clinical benefit to patients with DMD.

8 Review of Safety

8.1. Safety Review Approach

The analyses of deflazacort clinical safety were largely based on the two main safety and efficacy Phase 3 studies in DMD patients, MP-104-NM-001 and MP-104-NM-002. Additional safety data that were integrated for analysis are from the studies below. The available narratives for deaths, serious adverse events, laboratory studies, and vital signs were reviewed. The medical scientific literature was searched where appropriate for additional information, including published serious adverse events related to deflazacort. The Phase 1 studies had small populations, short treatment durations, and small drug doses, yielding correspondingly limited safety information and therefore form only a small part of the safety review.

- 4 single-dose Phase 1 studies in subjects who did not have DMD
  - MP-104-CL-023 (Pharmacokinetics)
  - MP-104-CL-024 (Pharmacokinetics)

– MP-104-CL-025 (Pharmacokinetics)
– MP-104-CL-026 (Bioavailability, food effect)
• 1 Phase 1 study in patients with DMD
– MP-104-CL-005 (Pharmacokinetics)
• 5 Phase 3 studies in patients with DMD
– MP-104-NM-001 (multicenter, double-blind, randomized, parallel-group, placebo controlled)
– MP-104-NM-057 (52-week extension of NM-001, but only AE data are available)
– MP-104-NM-002 (multicenter, double-blind, randomized, parallel-group, placebo controlled)
– MP-104-CL-022OLE (multicenter, open-label, extension study)
– MP-104-CL-037 (Open-label expanded access program)
– IND Safety Reports

For additional details about these studies, the reader is referred to Sections 5.1 and 13.3

In addition to the multiple adverse events known to be associated with corticosteroid use, the following safety issues are of particular relevance due to their potential severity :

• Gastrointestinal inflammatory conditions
• Glaucoma
• Liver failure
• Psychiatric complications
• Hypertension
• Cataracts
• Osteoporosis
• Metabolic/nutritional

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The size and subject duration of exposure for the deflazacort safety population are described in the following tables.

Table 57: Deflazacort Safety Population. Size and Denominators

Safety Database for Deflazacort Individuals exposed to deflazacort in this development program for Duchenne Muscular Dystrophy N= 319			
Clinical Trial Groups	Deflazacort (n= 319)	Prednisone (n= 63)	Placebo (n= 61)
Volunteers without DMD (Includes healthy, hepatic, and renally impaired groups)	135	0	0
Controlled trials conducted for DMD	151	63	61
All other than controlled trials conducted for DMD	33	0	0
Controlled trials conducted for other indications[4]	0	0	0

Source: Summary of Clinical Safety, Tables 1, 2 and 5.

Table 58. Deflazacort Safety Population. Duration of Exposure

Number of patients exposed to deflazacort:				
>=7 days	>= 91 days	>=181 days	>= 271 days	>=361 days
N= 158	N= 143	N= 125	N= 104	N= 62

Source: Summary of Clinical Safety, Table 12.

When compared to International Conference on Harmonisation (ICH) guidelines,[1] the overall number of exposed subjects is less than the usual recommendation. However, because DMD is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety. The number of subjects exposed ≥6 months nearly meets the ICH recommendation, and the number of subjects exposed ≥ 1 year exceeds the recommendation.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious. (ICH E-1)

8.2.2. Relevant characteristics of the safety population:

As described in the summary of clinical safety, all DMD patients in the studies were male, ranging in age from 5 to 15 years. The mean (SD) age of subjects who received deflazacort, prednisone 0.75 mg/kg/day, and placebo was 8.9 (2.89), 8.6 (2.96), and 8.3 (2.87) years, respectively. Subgroup analyses by ethnicity and race are not presented for the DMD patients pooled group because the overwhelming majority of subjects were white and the race of subjects in MP-104-NM-002 was not collected. For the pivotal study MP-104-NM-001, 94.4% of patients were white, 0.5% Asian, and 5.1% were listed as "other." Ethnicity was unknown for nearly all subjects except for 25 subjects treated with deflazacort 0.9 mg/kg/day (7 Hispanic or Latino and 18 not Hispanic or Latino).

8.2.3. Adequacy of the safety database:

Because DMD is a rare and terminal illness, the overall subject exposure in the clinical development program is adequate. Duration of treatment and patient demographics are acceptable. Other than anecdotal reports in the literature (Merlini et al., 2012), deflazacort safety information in patients younger than the minimum studied age of 5 years is lacking. Discussion with the pharmacology reviewer suggests that pharmacokinetics could be extrapolated down to age 2 years. Note that in clinical practice, the average age of initiating corticosteroid treatment (prednisone) in DMD patients is 9.36 years [SD 2.86] (Gloss et al., 2016). Although the Phase 3 studies had no safety data for patients older than the maximum studied age of 15, some safety data are available for adult subjects from the Phase 1 studies. There are also arguments for the extrapolation of pharmacokinetic data from 15 year-old patients to older teenagers and adults.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The NDA submission was well-organized. Requests for additional information were handled promptly by the applicant.

There were multiple issues related to the age of the clinical studies, including missing case report forms and missing data matching subjects to clinical sites, which prevented inspections of clinical study sites. As discussed further in Section 6.1.1, some safety assessments, such as laboratory results, vital signs, and concomitant medications in Study NM-002, could not be performed because the original study data were lost. There was also potential confusion in coding the DMD-associated loss of ambulation in Study NM-002, which triggered expulsion of a patient from the study, as "abasia," which is the inability to walk caused by a defect in muscular coordination (Merriam-Webster, 2016).

8.3.2. Categorization of Adverse Events

The applicant's process for recording AEs was appropriate. The applicant's coding resulted inappropriate translation of verbatim terms to MedDRA preferred terms.

The applicant categorized adverse events as mild, moderate, or severe. Adverse events were coded to MedDRA 16.1 for the two key safety and efficacy studies MP-104-NM-001 and MP-104-NM-002.

The number and percent of subjects who reported treatment-emergent adverse events (TEAEs), grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term are tabulated overall, by severity (mild, moderate, or severe), and by relationship to study drug (related or not related). If a TEAE was missing the severity and/or relationship, then the strongest possible severity or relationship was assumed for the analysis (ISS, p. 51).

8.3.3. Routine Clinical Tests

The laboratory assessment schedule for the pivotal safety/efficacy Study MP-104-NM-001 consisted of hematology, serum chemistry, and urinalysis at baseline and weeks 6 and 24. Growth hormone, insulin-like growth factor, and bone and metabolic markers were collected at baseline and weeks 12 and 52.

For Study MP-104-NM-002, the laboratory assessment schedule is not included in the original Italian or translated English language protocol. Assessments included hematology with white blood cell and platelet counts, fasting glycemia profile, electrolyte levels (Na, K, Ca; P) and CPK. Diagnostic tests included ECG, chest x-ray, left hand and wrist x-ray (bone age), as well as an eye exam checking for cataracts at the end of the trial. Based on individual patient data points, laboratory testing frequency was approximately every 2 months.

Reviewer comment: In the opinion of this reviewer, more frequent laboratory safety monitoring in Study MP-104-NM-001 would have been advisable. The approximately two-month laboratory assessment interval for Study MP-104-NM-002 appears acceptable, although more frequent cataract monitoring would have been advisable, as well.

8.4. Safety Results

8.4.1. Deaths

No subjects died in the Phase 1 studies.

One 14 year-old DMD patient died in the deflazacort treatment group of Study MP-104-NM-001 eight days into the study as a result of "an exacerbation of symptoms related to Duchenne Muscular Dystrophy." He was found deceased in bed at home following 24 hours of a febrile illness with upper respiratory tract infection. One DMD patient died in the deflazacort treatment group of Study MP-104-NM-001 after study completion due to accidental asphyxia from a rope around the neck while playing.

One DMD patient died in the prednisone treatment group from cardiomyopathy, which is a known complication of DMD.

Two adult patients (ages 69 and 75) being treated with deflazacort for rheumatoid arthritis died of Kaposi's sarcoma and "sudden death," respectively.

Reviewer Comment: It is unclear if the death of the first DMD patient is related to deflazacort use. Corticosteroids, including deflazacort, can suppress the body's ability to fight infection and this patient reportedly died while suffering from a febrile illness with upper respiratory tract infection. However, significant immune suppression is usually only related to chronic steroid use, whereas this patient reportedly died only 8 days after starting deflazacort. The accidental cause of death after study completion of the second DMD patient appears to be unrelated to the previous deflazacort use. The relationship of deflazacort to the deaths of the two adult rheumatoid arthritis patients is unclear. Advanced age or corticosteroid-related immunosuppression can lead to Kaposi's sarcoma. The cause of "sudden death" in the 75 year old woman who died 39 days after starting deflazacort is unknown.

8.4.2. Serious Adverse Events

Serious adverse events (SAEs) from the Integrated Summary of Safety (ISS) pool of all subjects that received deflazacort are summarized in the table below. Twenty (6.3%) of the 319 subjects who received deflazacort had at least one SAE, compared to 8 (13.1%) of the 61 placebo patients who had at least one SAE. Note that abasia and gait disturbance, which form nearly all placebo patient SAEs, have similar meanings and may both be related to DMD. Review of verbatim terms showed that abasia was used to refer to the loss of ambulation in subjects.

Note the larger SAE rate of 44.4% in the deflazacort 2mg/kg alternate day dosing group compared to 2.2% and 0% in the 0.9mg/kg and 1.2mg/kg groups, respectively. *This difference is misleading, however, because Study NM-002, which was the only study with a 2mg/kg alternate day dose, continued for more than 2 years compared to the 52 weeks of study NM-001. There was therefore a much longer time in study NM-002 for patients to accumulate AEs and SAEs and for the disease to progress.* More than half of the SAEs in the 2mg/kg alternate day group were from "abasia", defined in the study to indicate loss of ambulation, which occurs over time in DMD patients.

Table 59: Incidence of Treatment-emergent SAEs among all subjects who received deflazacort, listed in descending order of incidence by MedDRA preferred term

Incidence of Treatment-emergent SAEs, All Subjects

Preferred Term	Phase 1 Single-Dose Deflazacort (N = 135)	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 319)
Number of subjects with at least 1 SAE	0 (0.0%)	2 (2.2%)	0 (0.0%)	8 (44.4%)	1 (1.6%)	8 (13.1%)	20 (6.3%)
Abasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	8 (13.1%)	5 (1.6%)
Tendon disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
Erythema multiforme	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Appendicectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Asphyxia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Asthma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Biopsy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Bone development abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Burns third degree	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Compression fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Coma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Duchenne muscular dystrophy	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Encephalitis	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Gait disturbance	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (1.6%)	1 (0.3%)
Hyponatraemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Kaposi's sarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Migraine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Musculoskeletal disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Respiratory failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Substance-induced psychotic disorder	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Sudden death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Tenotomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (1.6%)	1 (0.3%)
Tracheostomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Toxic epidermal necrolysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Investigation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)

Source: ISS Table 4.3.6.1.
SAE = serious adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for the coding of AEs. AEs from the IND safety reports are represented in the total deflazacort column only.

Reviewer comment: I reviewed subject narratives, as well as other documents as necessary, in the assessment of the clinical study SAEs. There were no adverse events of aplastic anemia, pancytopenia, acute pancreatitis, torsade de pointes or other cardiac arrhythmia, or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome reported in the clinical development program.

There is a published report (Borras-Blasco et al., 2003) of Stevens-Johnson Syndrome in a patient taking multiple medications including sulfasalazine and deflazacort.

There are six reported cases of toxic epidermal necrolysis related to deflazacort use. One case is reported in the ISS in an eleven year-old girl who received deflazacort for myasthenia gravis. Two pediatric cases in the setting of nephrotic syndrome are described in a published report (Lee et al., 2014). A fourth case is reported in Navarro et al. (1996). The fifth and sixth cases are reported in Kim (2006) and Kim (2010). All of the reported cases resolved after stopping deflazacort treatment. There are also two reports of erythema multiforme related to deflazacort in the ISS.

Table 60: Six case reports of Toxic Epidermal Necrolysis (TENS) associated with deflazacort.

Patient	**Reason for deflazacort use**	**Medications (*italic* indicates deflazacort was sole medication)**	**Deflazacort treatment duration until TENS**
24 y.o. F	*myopia*	*deflazacort 90mg/day*	*3 weeks*
11 y.o. F	*myasthenia gravis*	*deflazacort 180mg/day*	*1.5 months*
11 y.o. M	*nephrotic syndrome*	*deflazacort 72mg/day*	*8 weeks*
14 y.o. M	nephrotic syndrome	deflazacort 24mg/tid (72mg total); risperidone (chronic) (0.5 mg,BID), atomoxetine (chronic)	17 days

		(25mgQD)	
4 y.o. M	nephrotic syndrome	deflazacort 24mg/tid (72mg total); enalapril(5mgQD)	41 days
14 y.o. M	membranous nephropathy	deflazacort 72mg/day, enalapril 5mg	2 weeks

One DMD patient was found to have asymptomatic vertebral compression fractures upon scoliosis screening while on compassionate use deflazacort. Osteoporosis that could lead to fractures is a known long-term effect of steroid use.

One DMD patient receiving deflazacort developed a psychotic disorder in the setting of encephalitis on day 421 in Study MP-104-NM-001. Psychosis is a known possible adverse effect of treatment with corticosteroids.

One reported cardiac arrest with coma was in the setting of emergency appendectomy and does not appear to be related to study drug. However, few details of this case from the Italian Study MP-104-NM-002 are available. Corticosteroids are not known to be causally related to appendicitis.

The reported "tendon disorders" are described as "congenital" and appear to be related to muscle and tendon contractures which are known to occur in DMD.

One patient developed severe migraine headache while on deflazacort to treat asthma. She had a history of migraine headaches for several years and reported prior migraine headache triggered by prednisone. Headache is a common reaction to prednisone and was also a common adverse event for deflazacort, although corticosteroids have been used in the treatment of migraine headaches. Given that asthma may increase the risk of migraine headache (Peng et al., 2016; Martin et al., 2016), it is unclear if deflazacort triggered a migraine or if the common headache from deflazacort exacerbated an existing migraine attack.

With the exception of the skin hypersensitivity reactions, the SAEs discussed above generally reflect either known corticosteroid-related effects or the results of the disease process underlying DMD.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No TEAE leading to permanent discontinuation of study treatment occurred in the Phase 1 single-dose pooled group

For the two pivotal Phase 3 studies, the number [percentage] of subjects with TEAEs leading to permanent discontinuation of deflazacort was 18 subjects [10.2%] with 5 subjects [5.4%] treated with deflazacort 0.9 mg/kg/day, 3 subjects [4.6%] treated with deflazacort 1.2 mg/kg/day, and 10 subjects [55.6%] treated with deflazacort 2 mg/kg alternate days). In comparison, 8 placebo subjects [13.1%] discontinued due to TEAEs.

The most commonly reported TEAE leading to permanent discontinuation among all subjects who received deflazacort was abasia (verbatim term was loss of ambulation) (4 subjects all from study NM-002 [2.3%] total deflazacort, 8 subjects [13.1%] placebo) and weight increased (4 subjects [2.3%] total deflazacort, no placebo subjects). Discontinuation from Study MP-104-NM-002 was required following loss of ambulation.
(Summary of Clinical Safety, p. 95)

Reviewer Comment: Deflazacort 2mg/kg alternate days had a 55.6% dropout rate due to TEAE, compared to 5.4% at 0.9 mg/kg/day and 4.6% at 1.2 mg/kg/day, arguing against the use of the 2mg/kg altern3ate day dosing. However, the 2mg/kg dosing regimen was maintained for a longer time (>2 years), allowing more dropouts to be observed. It is unclear why discontinuation from Study MP-104-NM-002 was required following loss of ambulation, since other strength measurements could still have been made. Note that Study MP-104-NM-001 included non-ambulatory patients.

I have reviewed the clinical study criteria for stopping treatment. In the opinion of this reviewer, the criteria were appropriate except for Study MP-104-NM-002, for which no stopping criteria were listed in the protocol.

Table 61: Summary of adverse events leading to permanent treatment discontinuation

Incidence of TEAEs Leading to Permanent Discontinuation of Study Treatment, All Subjects

Preferred Term	Phase 1 Single-Dose Deflazacort (N = 135)	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 319)
Number of subjects with at least 1 TEAE leading to permanent discontinuation of study treatment	0 (0.0%)	5 (5.4%)	3 (4.6%)	10 (55.6%)	4 (6.3%)	8 (13.1%)	24 (7.5%)
Abasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)	0 (0.0%)	8 (13.1%)	4 (1.3%)
Weight increased	0 (0.0%)	2 (2.2%)	2 (3.1%)	0 (0.0%)	2 (3.2%)	0 (0.0%)	4 (1.3%)
Abdominal pain upper	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Aggression	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Appendicectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Asphyxia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Biopsy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Blood potassium decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cataract	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Central obesity	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.3%)
Cushingoid	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Duchenne muscular dystrophy	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Erythema	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Erythema multiforme	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Kaposi's sarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Migraine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Obesity	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Refusal of treatment by patient	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Refusal of treatment by relative	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Respiratory failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Sleep disorder	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Sudden death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Tendon disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Toxic epidermal necrolysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Tracheostomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Treatment noncompliance	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Tenotomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)

Source: ISS Table 4.3.4.1.
TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for the coding of AEs. AEs from IND safety reports are represented in the total deflazacort column only.

8.4.4. Significant Adverse Events

The applicant categorized clinical study adverse events by severity (mild, moderate, or severe) in the integrated summary of safety datasets, as described in Section 8.3.2. Sixty-eight of the 319 subjects (21.3%) who received deflazacort had severe adverse events, compared to 14 of the 61 (23%) placebo subjects. Adverse events categorized as severe are discussed in the serious adverse event assessment and in Section 8.5: Submission-Specific Safety Issues.

Table 62: Adverse Event Summary by Severity

Overview of Summary AEs, All Subjects (Source: Summary of Clinical Safety, p. 54)

Parameter	Phase 1 Single-Dose Deflazacort (N = 135)	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 319)
Number of subjects with at least 1 TEAE	28 (20.7%)	76 (81.7%)	56 (86.2%)	14 (77.8%)	58 (92.1%)	46 (75.4%)	182 (57.1%)
Mild TEAE	24 (17.8%)	22 (23.7%)	7 (10.8%)	2 (11.1%)	10 (15.9%)	19 (31.1%)	55 (17.2%)
Moderate TEAE	4 (3.0%)	33 (35.5%)	22 (33.8%)	1 (5.6%)	20 (31.7%)	13 (21.3%)	59 (18.5%)
Severe TEAE	0 (0.0%)	21 (22.6%)	27 (41.5%)	11 (61.1%)	28 (44.4%)	14 (23.0%)	68 (21.3%)
Number of subjects with at least 1 SAE	0 (0.0%)	2 (2.2%)	0 (0.0%)	8 (44.4%)	1 (1.6%)	8 (13.1%)	20 (6.3%)
Number of subjects with at least 1 TEAE leading to permanent discontinuation of study treatment	0 (0.0%)	5 (5.4%)	3 (4.6%)	10 (55.6%)	4 (6.3%)	8 (13.1%)	24 (7.5%)
Number of subjects with at least 1 TEAE causing death	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	4 (1.3%)

Source: ISS Table 4.3.1.1, Table 4.3.2.1, Table 4.3.4.1, Table 4.3.5.1, Table 4.3.6.1.
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Subjects from IND safety reports are represented in the total deflazacort column only.

(Summary of Clinical Safety, p. 54)

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs among all subjects who received deflazacort are listed in the following table taken from the applicant. Note that the total rate of TEAE in patients who received deflazacort differs based on whether the Phase 1 patients are included (57.1%) or not (83%). The 83% rate probably more accurately reflects the TEAE rate to be expected in DMD patients receiving regular deflazacort dosing as opposed to the single doses used in the Phase 1 studies. Tables with and without the Phase 1 studies are included for comparison below. Descriptive comparison of the 0.9mg/kg/day and 1.2 mg/kg/day arms of Study MP-104-NM-001 shows similar rates of TEAE (81.7% vs. 86.2%, respectively), with greater

rates of Cushingoid appearance (44.1% vs. 69.2%, respectively) and severe TEAE in the 1.2mg/kg/day arm (22.6% vs. 41.5%, respectively; Section 8.4.4 table). TEAE comparison between the 2mg/kg alternate day dosing and the daily dosing regimen is difficult because of the longer 2-3 year duration of the 2mg/kg alternate day regimen (Study MP-104-NM-002) which may have allowed more TEAEs to be recorded. The data suggest that there may be fewer Cushingoid TEAEs (16.7%) in the 2mg/kg/day alternate day dosing, but with more abasia and weakness than the 0.9mg/kg/day or 1.2mg/kg/day doses (27.8% at 2mg/kg alternate day vs. 0% at 0.9 or 1.2mg/kg/day). As discussed in Section 8.4.3, there were also more dropouts at the 2mg/kg alternate day dose, although the difference in study durations makes this comparison problematic. The rates of headache were similar in the placebo and deflazacort groups (19.7% and 22.7%, respectively).

Table 63: Common Adverse Events across studies in DMD patients (Source: Summary of Clinical Safety, p. 57)

Incidence of TEAEs in ≥ 10% of Subjects in Any Treatment Group, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE	76 (81.7%)	56 (86.2%)	14 (77.8%)	58 (92.1%)	46 (75.4%)	146 (83.0%)
Cushingoid	41 (44.1%)	45 (69.2%)	3 (16.7%)	49 (77.8%)	5 (8.2%)	89 (50.6%)
Erythema	19 (20.4%)	34 (52.3%)	0 (0.0%)	33 (52.4%)	3 (4.9%)	53 (30.1%)
Hirsutism	24 (25.8%)	25 (38.5%)	3 (16.7%)	29 (46.0%)	1 (1.6%)	52 (29.5%)
Weight increased	21 (22.6%)	20 (30.8%)	1 (5.6%)	22 (34.9%)	3 (4.9%)	42 (23.9%)
Headache	17 (18.3%)	22 (33.8%)	1 (5.6%)	22 (34.9%)	12 (19.7%)	40 (22.7%)
Nasopharyngitis	21 (22.6%)	15 (23.1%)	0 (0.0%)	11 (17.5%)	3 (4.9%)	36 (20.5%)
Central obesity	17 (18.3%)	16 (24.6%)	0 (0.0%)	27 (42.9%)	2 (3.3%)	33 (18.8%)
Increased appetite	11 (11.8%)	8 (12.3%)	2 (11.1%)	12 (19.0%)	1 (1.6%)	21 (11.9%)
Pollakiuria	12 (12.9%)	9 (13.8%)	0 (0.0%)	3 (4.8%)	1 (1.6%)	21 (11.9%)
Abdominal pain upper	9 (9.7%)	9 (13.8%)	1 (5.6%)	10 (15.9%)	4 (6.6%)	19 (10.8%)
Constipation	7 (7.5%)	10 (15.4%)	0 (0.0%)	4 (6.3%)	3 (4.9%)	17 (9.7%)
Upper respiratory tract infection	10 (10.8%)	7 (10.8%)	0 (0.0%)	7 (11.1%)	5 (8.2%)	17 (9.7%)
Influenza	4 (4.3%)	12 (18.5%)	0 (0.0%)	10 (15.9%)	2 (3.3%)	16 (9.1%)
Cough	7 (7.5%)	8 (12.3%)	0 (0.0%)	8 (12.7%)	3 (4.9%)	15 (8.5%)
Abnormal behaviour	7 (7.5%)	4 (6.2%)	1 (5.6%)	9 (14.3%)	3 (4.9%)	12 (6.8%)
Rash	5 (5.4%)	7 (10.8%)	0 (0.0%)	2 (3.2%)	3 (4.9%)	12 (6.8%)
Skin striae	4 (4.3%)	8 (12.3%)	0 (0.0%)	7 (11.1%)	0 (0.0%)	12 (6.8%)
Acne	4 (4.3%)	7 (10.8%)	0 (0.0%)	4 (6.3%)	1 (1.6%)	11 (6.3%)
Nausea	4 (4.3%)	7 (10.8%)	0 (0.0%)	2 (3.2%)	2 (3.3%)	11 (6.3%)
Vomiting	2 (2.2%)	7 (10.8%)	0 (0.0%)	6 (9.5%)	4 (6.6%)	9 (5.1%)
Ear infection	2 (2.2%)	6 (9.2%)	0 (0.0%)	7 (11.1%)	1 (1.6%)	8 (4.5%)
Diarrhoea	4 (4.3%)	3 (4.6%)	0 (0.0%)	9 (14.3%)	4 (6.6%)	7 (4.0%)
Abasia	0 (0.0%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	8 (13.1%)	5 (2.8%)
Muscular weakness	0 (0.0%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	0 (0.0%)	5 (2.8%)
Fall	2 (2.2%)	0 (0.0%)	2 (11.1%)	1 (1.6%)	1 (1.6%)	4 (2.3%)
Tendon disorder	0 (0.0%)	0 (0.0%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	4 (2.3%)
Appetite disorder	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	1 (1.6%)	3 (1.7%)
Osteopenia	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	3 (1.7%)

Source: ISS Table 4.2.1.1.
DMD = Duchenne muscular dystrophy; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once.

Table 64: Common Adverse Events across studies in ALL subjects who received deflazacort (Source: Integrated Summary of Safety, p. 61)

Incidence of TEAEs in ≥ 10% of Subjects in Any Treatment Group, All Subjects

Preferred Term	Phase 1 Single-Dose Deflazacort (N = 135)	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 319)
Number of subjects with at least 1 TEAE	28 (20.7%)	76 (81.7%)	56 (86.2%)	14 (77.8%)	58 (92.1%)	46 (75.4%)	182 (57.1%)
Cushingoid	0 (0.0%)	41 (44.1%)	45 (69.2%)	3 (16.7%)	49 (77.8%)	5 (8.2%)	89 (27.9%)
Headache	13 (9.6%)	17 (18.3%)	22 (33.8%)	1 (5.6%)	22 (34.9%)	12 (19.7%)	53 (16.6%)
Erythema	0 (0.0%)	19 (20.4%)	34 (52.3%)	0 (0.0%)	33 (52.4%)	3 (4.9%)	53 (16.6%)
Hirsutism	0 (0.0%)	24 (25.8%)	25 (38.5%)	3 (16.7%)	29 (46.0%)	1 (1.6%)	52 (16.3%)
Weight increased	0 (0.0%)	21 (22.6%)	20 (30.8%)	1 (5.6%)	22 (34.9%)	3 (4.9%)	42 (13.2%)
Nasopharyngitis	0 (0.0%)	21 (22.6%)	15 (23.1%)	0 (0.0%)	11 (17.5%)	3 (4.9%)	36 (11.3%)
Central obesity	0 (0.0%)	17 (18.3%)	16 (24.6%)	0 (0.0%)	27 (42.9%)	2 (3.3%)	33 (10.3%)
Increased appetite	0 (0.0%)	11 (11.8%)	8 (12.3%)	2 (11.1%)	12 (19.0%)	1 (1.6%)	21 (6.6%)
Pollakiuria	0 (0.0%)	12 (12.9%)	9 (13.8%)	0 (0.0%)	3 (4.8%)	1 (1.6%)	21 (6.6%)
Abdominal pain upper	0 (0.0%)	9 (9.7%)	9 (13.8%)	1 (5.6%)	10 (15.9%)	4 (6.6%)	19 (6.0%)
Constipation	2 (1.5%)	7 (7.5%)	10 (15.4%)	0 (0.0%)	4 (6.3%)	3 (4.9%)	19 (6.0%)
Upper respiratory tract infection	1 (0.7%)	10 (10.8%)	7 (10.8%)	0 (0.0%)	7 (11.1%)	5 (8.2%)	18 (5.6%)
Influenza	0 (0.0%)	4 (4.3%)	12 (18.5%)	0 (0.0%)	10 (15.9%)	2 (3.3%)	16 (5.0%)
Cough	0 (0.0%)	7 (7.5%)	8 (12.3%)	0 (0.0%)	8 (12.7%)	3 (4.9%)	15 (4.7%)
Nausea	3 (2.2%)	4 (4.3%)	7 (10.8%)	0 (0.0%)	2 (3.2%)	2 (3.3%)	14 (4.4%)
Abnormal behaviour	0 (0.0%)	7 (7.5%)	4 (6.2%)	1 (5.6%)	9 (14.3%)	3 (4.9%)	12 (3.8%)
Rash	0 (0.0%)	5 (5.4%)	7 (10.8%)	0 (0.0%)	2 (3.2%)	3 (4.9%)	12 (3.8%)
Skin striae	0 (0.0%)	4 (4.3%)	8 (12.3%)	0 (0.0%)	7 (11.1%)	0 (0.0%)	12 (3.8%)
Acne	0 (0.0%)	4 (4.3%)	7 (10.8%)	0 (0.0%)	4 (6.3%)	1 (1.6%)	11 (3.4%)
Vomiting	0 (0.0%)	2 (2.2%)	7 (10.8%)	0 (0.0%)	6 (9.5%)	4 (6.6%)	9 (2.8%)
Diarrhoea	1 (0.7%)	4 (4.3%)	3 (4.6%)	0 (0.0%)	9 (14.3%)	4 (6.6%)	8 (2.5%)
Ear infection	0 (0.0%)	2 (2.2%)	6 (9.2%)	0 (0.0%)	7 (11.1%)	1 (1.6%)	8 (2.5%)
Abasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	8 (13.1%)	5 (1.6%)
Muscular weakness	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	0 (0.0%)	5 (1.6%)
Fall	0 (0.0%)	2 (2.2%)	0 (0.0%)	2 (11.1%)	1 (1.6%)	1 (1.6%)	4 (1.3%)
Tendon disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	4 (1.3%)
Appetite disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	1 (1.6%)	3 (0.9%)
Osteopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	3 (0.9%)

Source: ISS Table 4.3.1.1.
TEAE = treatment-emergent adverse events.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for the coding of AEs. AEs from IND safety reports are represented in the total deflazacort column only.
Note: for subjects in Study MP-104-CL-025, all AEs with a start date/time post dosing with study drug in Treatment Period 1 or the last day of Treatment Period 2 (combined drug) are summarized under Phase 1 Single-Dose deflazacort.

Analyses of MAED and MedDRA terms with comparisons to placebo support the findings in the table above, suggesting increased rates in the deflazacort group of Cushingoid appearance,

increased weight, central obesity, hirsutism, upper respiratory tract infections, mood disorders, and pollakiuria. Including the 2-year study NM-002 also finds increased rates of osteopenia, tendon disorder, muscle weakness, and falls in the deflazacort group relative to placebo, although interpretation of these findings is complicated by the loss of most placebo (only 3 remaining) patients by 2 years of Study NM-002. It is notable that more (8/11, ~73%) DMD patients in the placebo group of Study NM-002 lost ambulation and were therefore discontinued from the study than in the deflazacort group (5/18, ~28%). MAED preferred terms that occurred in at least two patients in the deflazacort group in Studies MP-104-NM-001 and NM-002 compared to placebo are shown in the tables below.

Table 65: MAED preferred terms in deflazacort group in 2 or more patients versus placebo, weeks 1-12 of Study MP-104-NM-001.

	Group ID 1: Deflazacort (N = 100)			Placebo (N = 50)		
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Cushingoid	40	34	34	6	6	12
Weight increased	21	19	19	2	2	4
Headache	27	17	17	23	10	20
Increased appetite	13	13	13	1	1	2
Pollakiuria (urinary frequency)	16	12	12	1	1	2
Erythema	13	12	12	4	3	6
Central obesity	16	11	11	2	2	4
Hirsutism	9	9	9	1	1	2
Nasopharyngitis	12	9	9	3	3	6
Abdominal pain upper	13	9	9	4	4	8
Cough	10	8	8	4	3	6
Abdominal discomfort	7	7	7	1	1	2
Abdominal pain	9	7	7	3	3	6
Acne	7	6	6	1	1	2
Upper respiratory tract infection	6	6	6	5	5	10
Nausea	6	5	5	2	2	4
Rhinorrhoea	4	4	4	0	0	0
Influenza	5	4	4	2	2	4
Constipation	4	4	4	3	3	6
Viral infection	3	3	3	0	0	0
Aggression	3	3	3	1	1	2
Contusion	3	3	3	1	1	2
Unevaluable event	3	3	3	1	1	2
Irritability	3	3	3	3	2	4
Otitis media	4	3	3	5	3	6
Vomiting	4	3	3	4	3	6
Dizziness	4	2	2	0	0	0
Dyspepsia	4	2	2	0	0	0
Affect lability	2	2	2	0	0	0

Mood swings	2	2	2	0	0	0
Pain in extremity	2	2	2	0	0	0
Pharyngitis	2	2	2	0	0	0
Sleep disorder	2	2	2	0	0	0
Polyuria	5	2	2	1	1	2
Psychomotor hyperactivity	2	2	2	1	1	2
Respiratory disorder	2	2	2	1	1	2
Epistaxis	3	2	2	2	2	4
Abnormal behaviour	2	2	2	3	3	6
Rash	2	2	2	4	3	6
Pyrexia	2	2	2	6	4	8

Table 66: MAED preferred terms in deflazacort group in 2 or more patients versus placebo, 2 years of Study MP-104-NM-002 (Note: Abasia = Loss of ambulation)

	Deflazacort 2 mg/kg (N = 18)			*Placebo (N = 11)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Abasia	7	5	27.78	9	8	72.73
Increased appetite	8	4	22.22	0	0	0
Muscular weakness	4	4	22.22	0	0	0
Hirsutism	14	3	16.67	0	0	0
Cushing's syndrome	12	3	16.67	0	0	0
Osteopenia	4	3	16.67	0	0	0
Tendon disorder	3	3	16.67	0	0	0
Fall	2	2	11.11	1	1	9.09
Refusal of treatment by patient	2	2	11.11	0	0	0

8.4.6. Laboratory Findings

Laboratory findings for patients who received deflazacort in the Phase 1 studies and in the main efficacy and safety study NM-001 are discussed below. Blood and urine samples for laboratory safety tests (hematology, serum chemistry, and urinalysis) were taken at Screening, Week 6, Week 24, and Week 52. Note that the placebo group was switched to active drug at week 12 and was therefore on active drug for the laboratory tests at weeks 24 and 52. Analysis of laboratory data for patients in study NM-002 is not possible due to missing data.

In the Phase 1 Single-Dose pooled group, mean blood chemistry and hematology values at day 2 post-treatment were similar to Baseline, with no clinically significant changes as shown in the table below.

Table 67: Phase 1 Single-Dose Pooled Laboratory and Hematology Changes from Baseline (Source: Integrated Summary of Safety, p. 145)

Phase 1 Study Laboratory and Hematology Tests	Total Deflazacort Group (N=135): Mean (SD) Change from Baseline to Day 2, Post-Treatment
ALT (U/L)	-2.5 (4.72)
Albumin (g/L)	-0.1 (2.35)
Alkaline phosphatase (U/L)	-4.2 (7.78)
AST (U/L)	-3.4 (6.83)
Bicarbonate (mmol/L)	0.24 (2.735)
Bilirubin (umol/L)	0.591 (4.2041)
BUN (mmol/L)	0.206 (2.5178)
Calcium (mmol/L)	0.033 (0.0961)
Chloride (mmol/L)	0.9 (2.04)
Cholesterol (mmol/L)	0.174 (0.5693)
Creatinine (umol/L)	9.725 (68.3460)
Creatinine clearance (mL/min)	-1.47 (14.096)
Direct bilirubin (umol/L)	-0.176 (1.0950)
GGT (IU/L)	-1.4 (4.62)
Glucose (IU/L)	-0.021 (0.4750)
Lactate dehydrogenase (U/L)	-14.0 (26.90)
Phosphate (mmol/L)	0.117 (0.2253)
Potassium (mmol/L)	-0.09 (0.380)
Protein (g/L)	-0.1 (3.98)
Sodium (mmol/L)	0.3 (1.67)
Thyrotropin (mU/L)	0.984 (0.8314)
Triglycerides (mmol/L)	-0.211 (0.4740)
Urate (umol/L)	-23.0 (42.52)
Urea (mmol/L)	-0.03 (1.101)
Basophils (10^9/L)	0.005 (0.0255)
Basophils/leukocytes (%)	0.018 (0.4917)
Eosinophils (10^9/L)	-0.037 (0.0788)
Eosinophils/leukocytes (%)	-0.915 (1.5440)
Erythrocytes (1012/L)	0.006 (0.2232)
Hematocrit (L/L)	0.001 (0.0200)
HGB (g/L)	0.5 (6.61)
Leukocytes (10^9/L)	0.875 (1.4037)
Lymphocytes (10^9/L)	0.29 (0.408)
Lymphocytes/leukocytes (%)	0.028 (5.4572)
Monocytes (10^9/L)	0.082 (0.1416)
Monocytes/leukocytes (%)	0.047 (1.5520)

Neutrophils (10^9/L)	0.52 (1.088)
Neutrophils/leukocytes (%)	0.793 (6.6575)
Platelets (10^9/L)	6.4 (21.70)

The applicant reports that laboratory values at baseline were typical for patients with DMD, with elevated aspartate aminotransferase (AST), creatine kinase (CK), and lactate dehydrogenase (LDH). At Week 6 of Study NM-001, AST, LDH, and CK increased in the placebo group and significantly decreased with the 3 active treatments. At 52 weeks [with all patients on active drug], levels mostly remained below baseline with the largest sustained differences in the deflazacort 0.9 mg/kg/day group compared to the deflazacort 1.2 mg/kg/day and the prednisone group (Summary of Clinical Efficacy, p. 17). See section 6.1.2 for discussion of the relevance to efficacy.

Analysis of the submitted data suggested one possible Hy's Law case of a 14 year-old DMD patient (Study MP-104-NM001, subject 001-028) with abnormal liver function test results. *However, this patient had abnormally elevated liver function tests (AST, ALT, total bilirubin) as well as elevated creatine kinase at baseline screening prior to receiving deflazacort. Therefore, no clear connection with deflazacort can be made.* Given the normal alkaline phosphatase level and very high CK, the elevated LFTs are likely due to muscle damage from DMD. No other background history about this patient is known. His reported adverse events during the study included abdominal pain/stomach aches, greenstick fracture, pharyngitis, and Cushingoid appearance. His laboratory test results are shown in the following figure, taken from the patient data listings.

Figure 13: Laboratory values for patient 001-028. Source: patient data listings for Study MP-104-NM-001

Treatment: Deflazacort 1.2 mg/kg

Subject ID	Laboratory Subcategory	Laboratory Test	Time Point [1]	Collection Date/Time	Reason Not Done	Result/Flag [2]	Reference Range Low	Reference Range High	Test Units
001-028		Alanine Aminotransferase	Screening	31MAY1993:08:00:00		131 H	6	43	U/L
			Week 6	13JUL1993:09:25:00		102 H	6	43	U/L
			Week 24	16NOV1993:08:00:00		136 H	6	43	U/L
			Week 52/ET	30MAY1994:07:45:00		160 H	6	43	U/L
		Alkaline Phosphatase	Screening	31MAY1993:08:00:00		173	95	385	U/L
			Week 6	13JUL1993:09:25:00		126	95	385	U/L
			Week 24	16NOV1993:08:00:00		57	50	250	U/L
			Week 52/ET	30MAY1994:07:45:00		55	50	250	U/L
		Aspartate Aminotransferase	Screening	31MAY1993:08:00:00		83 H	11	36	U/L
			Week 6	13JUL1993:09:25:00		83 H	11	36	U/L
			Week 24	16NOV1993:08:00:00		69 H	11	36	U/L
			Week 52/ET	30MAY1994:07:45:00		84 H	11	36	U/L

Bilirubin	Screening	31MAY1993:08:00:00	26 H	3	21	umol/L
	Week 6	13JUL1993:09:25:00	26 H	3	21	umol/L
	Week 24	16NOV1993:08:00:00	31 H	3	21	umol/L
	Week 52/ET	30MAY1994:07:45:00	44 H	3	21	umol/L
Creatine Kinase	Screening	31MAY1993:08:00:00	3320 H	94	499	U/L
	Week 6	13JUL1993:09:25:00	2637 H	94	499	U/L
	Week 24	16NOV1993:08:00:00	2240 H	94	499	U/L
	Week 52/ET	30MAY1994:07:45:00	1637 H	94	499	U/L

Hematology

Mean baseline values and mean changes by study visit in the placebo-controlled Study MP-104-NM-001 are summarized in the figures below. There were no cases of clinically significant anemia, leukopenia, or thrombocytopenia. The applicant reports that in subjects in the DMD patients pooled group receiving 0.9 mg/kg/day or 1.2 mg/kg/day deflazacort with hematology values at both baseline and month 12, all hematology parameters were normal and remained normal at month 12 (ISS, p. 207). Baseline values were missing for the white blood cells. *For hematocrit and hemoglobin, there was a small increasing trend in the two deflazacort dose arms over 52 weeks, seen in the figures below, that was still within the normal range and is therefore not clinically concerning. Leukocytes appeared slightly higher in the deflazacort group compared to placebo at week 6, but were still within the normal range.*

Figure 14: Hematocrit: Mean with standard deviation per study arm by visit. Visit 1 = Screening. Visit 4 = 52 Weeks (Normal range: 40%-52% (men))

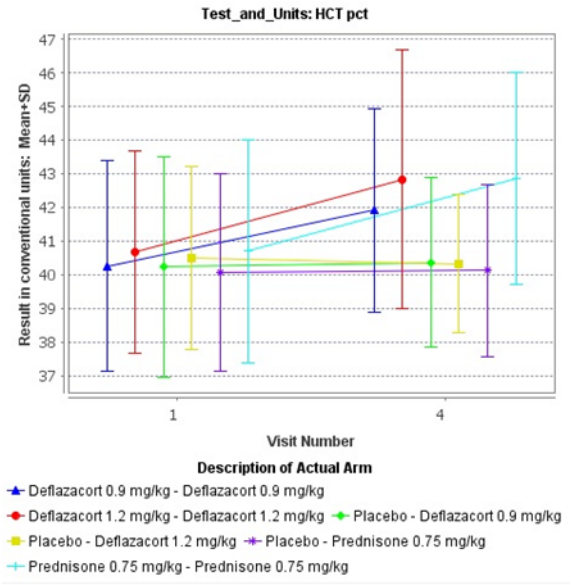


Table 68: Hematocrit summary statistics during placebo-control portion of Study NM-001. Source: NM-001 Body, p. 736

Summary Statistics of Hematology Laboratory Results by Visit to Week 6
Safety Population

Parameter Time Point [1] Statistic	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
Hematocrit (L/L)				
Baseline				
n	48	43	46	48
Mean (SD)	0.401 (0.0316)	0.407 (0.0310)	0.408 (0.0335)	0.403 (0.0297)
Median	0.400	0.410	0.400	0.400
Min, Max	0.34, 0.47	0.34, 0.47	0.33, 0.50	0.34, 0.46
Week 6				
n	48	42	43	46
Mean (SD)	0.419 (0.0301)	0.428 (0.0389)	0.429 (0.0314)	0.403 (0.0234)
Median	0.420	0.430	0.420	0.400
Min, Max	0.35, 0.48	0.34, 0.54	0.37, 0.52	0.35, 0.44
Final Assessment				
n	48	42	43	46
Mean (SD)	0.419 (0.0301)	0.428 (0.0389)	0.429 (0.0314)	0.403 (0.0234)
Median	0.420	0.430	0.420	0.400
Min, Max	0.35, 0.48	0.34, 0.54	0.37, 0.52	0.35, 0.44

[1] Final assessment is the last observed visit within the period.

Figure 15: Hemoglobin: Mean with standard deviation per study arm by visit (Normal range: 13-17 g/dL (men))

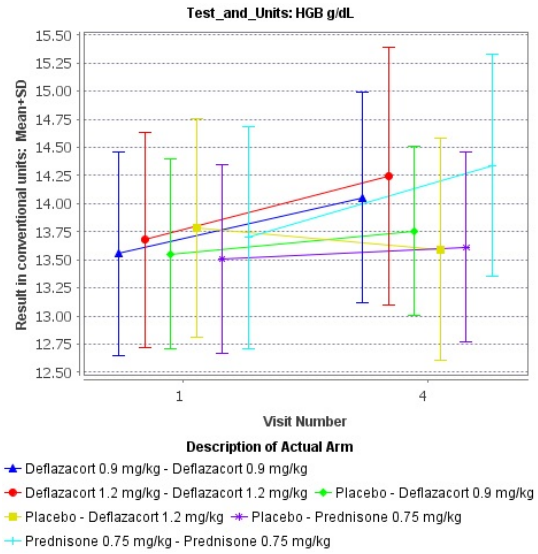


Table 69: Hemoglobin summary statistics during placebo-control portion of Study NM-001. Source: NM-001 Body, p. 737

Summary Statistics of Hematology Laboratory Results by Visit to Week 6
Safety Population

Parameter Time Point [1] Statistic	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
Hemoglobin (g/L)				
Baseline				
n	49	45	46	50
Mean (SD)	135.2 (9.36)	136.7 (9.73)	137.2 (10.02)	136.1 (8.91)
Median	136.0	137.0	135.5	135.0
Min, Max	115, 157	115, 161	110, 164	115, 161
Week 6				
n	48	43	46	47
Mean (SD)	140.5 (9.35)	142.3 (11.54)	143.4 (9.86)	136.6 (8.46)
Median	141.5	143.0	144.5	136.0
Min, Max	117, 161	118, 179	128, 172	116, 157
Final Assessment				
n	48	43	46	47
Mean (SD)	140.5 (9.35)	142.3 (11.54)	143.4 (9.86)	136.6 (8.46)
Median	141.5	143.0	144.5	136.0
Min, Max	117, 161	118, 179	128, 172	116, 157

[1] Final assessment is the last observed visit within the period.

Figure 16: Platelets: Mean with standard deviation per study arm by visit (Normal range: 150-400 x 10^9/L)

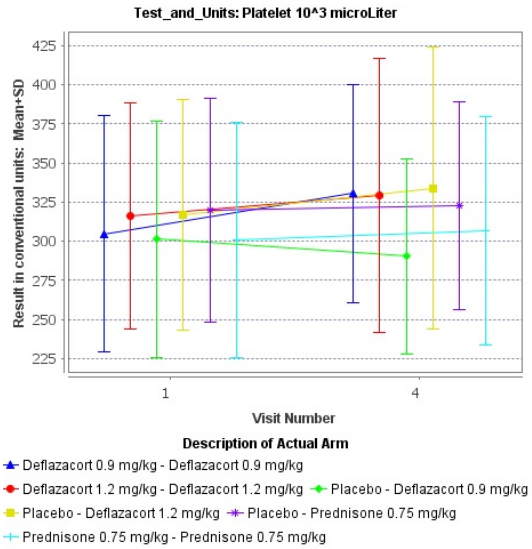


Table 70: Platelets summary statistics during placebo-control portion of Study NM-001. Source: NM-001 Body, p. 742

Summary Statistics of Hematology Laboratory Results by Visit to Week 6
Safety Population

Parameter Time Point [1] Statistic	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
Platelets (10^9/L)				
Baseline				
n	49	45	46	49
Mean (SD)	301.3 (69.40)	316.2 (70.18)	298.5 (75.46)	310.0 (72.86)
Median	290.0	319.0	296.5	311.0
Min, Max	159, 475	211, 516	152, 492	184, 442
Week 6				
n	48	43	46	47
Mean (SD)	330.5 (69.77)	331.3 (87.52)	306.6 (73.30)	315.3 (74.48)
Median	317.0	335.0	306.0	312.0
Min, Max	208, 497	158, 644	152, 515	186, 498
Final Assessment				
n	48	43	46	47
Mean (SD)	330.5 (69.77)	331.3 (87.52)	306.6 (73.30)	315.3 (74.48)
Median	317.0	335.0	306.0	312.0
Min, Max	208, 497	158, 644	152, 515	186, 498

[1] Final assessment is the last observed visit within the period.

Figure 17: White Blood Cells: Mean with standard deviation per study arm at visit 4. Baseline values missing. (Normal range: 4-10 x 10^9/L)

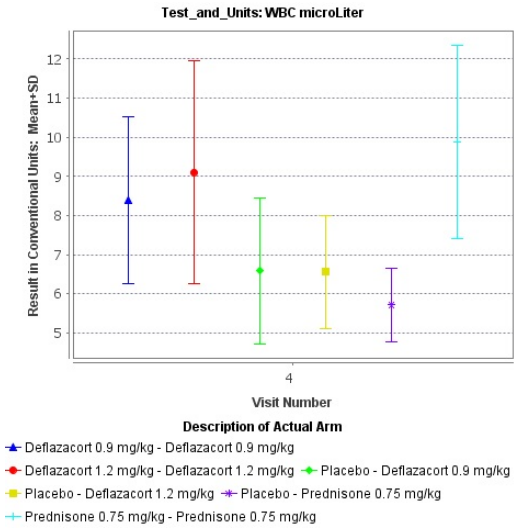


Table 71: White blood cells/leukocytes summary statistics during placebo-control portion of Study NM-001. Source: NM-001 Body, p. 738

Summary Statistics of Hematology Laboratory Results by Visit to Week 6
Safety Population

Parameter Time Point [1] Statistic	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
Leukocytes (10^9/L)				
Baseline				
n	49	45	46	50
Mean (SD)	5.980 (1.3281)	6.485 (1.7903)	5.929 (1.4952)	6.208 (1.8117)
Median	6.080	6.150	5.800	5.945
Min, Max	3.15, 8.74	3.95, 11.33	3.24, 10.31	3.76, 11.23
Week 6				
n	48	43	46	47
Mean (SD)	8.404 (2.1352)	9.113 (2.8878)	9.875 (2.4714)	6.276 (1.4885)
Median	8.605	8.510	9.400	6.050
Min, Max	4.67, 13.12	2.99, 17.08	5.02, 15.48	3.77, 10.14
Final Assessment				
n	48	43	46	47
Mean (SD)	8.404 (2.1352)	9.113 (2.8878)	9.875 (2.4714)	6.276 (1.4885)
Median	8.605	8.510	9.400	6.050
Min, Max	4.67, 13.12	2.99, 17.08	5.02, 15.48	3.77, 10.14

[1] Final assessment is the last observed visit within the period.

Clinical chemistry laboratory results

The applicant reports that in the DMD patients pooled group, for subjects receiving 0.9 mg/kg/day or 1.2 mg/kg/day deflazacort, the majority of parameters (albumin, bicarbonate, bilirubin, blood urea nitrogen [BUN], calcium, chloride, cholesterol, direct bilirubin, glucose, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, phosphate, potassium, protein, sodium, urate, and very low-density lipoprotein [VLDL] cholesterol) were normal, but with missing data for some patients at various time points [Screening, Week 6, Week 24, or Week 52] (ISS, p. 194).

Clinical chemistry laboratory results in the placebo-controlled Study MP-104-NM-001 are summarized in the figures below. There were many missing data points either at baseline or at follow-up that prevent meaningful assessment of changes from baseline. *There appears to be a trend of low serum calcium with elevated phosphate levels across all study arms.* Note that placebo patients switched to an active drug arm after week 12. Low serum calcium levels with high phosphate levels may be observed with renal failure, hypoparathyroidism, or pseudohypoparathyroidism. There was no evidence of renal failure in study patients. Parathyroid hormone levels were not measured. Glucocorticoids are known to increase renal

calcium excretion and decrease gastrointestinal calcium absorption, which can lead to low serum calcium levels.

Figure 18: Bicarbonate: Whiskers plot with outliers (Normal range 22 - 28 mEq/L)

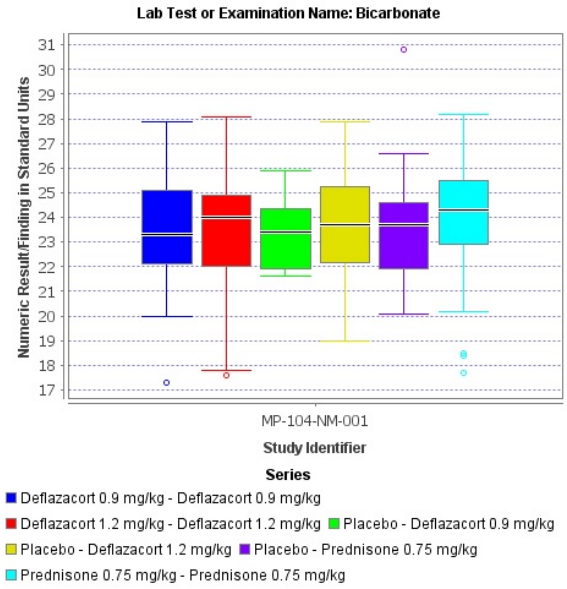


Figure 19: Calcium: Whiskers plot with outliers (Normal range 2-2.6 mmol/L)

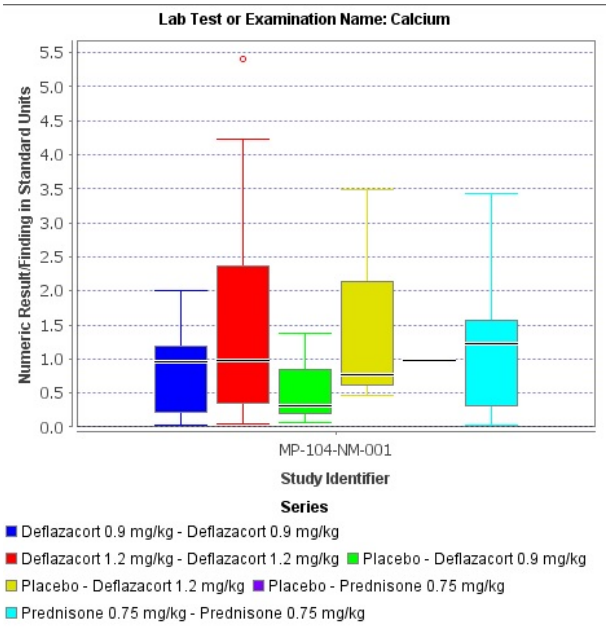


Figure 20: Sodium: Whiskers plot with outliers (Normal range 135-145 mmol/L)

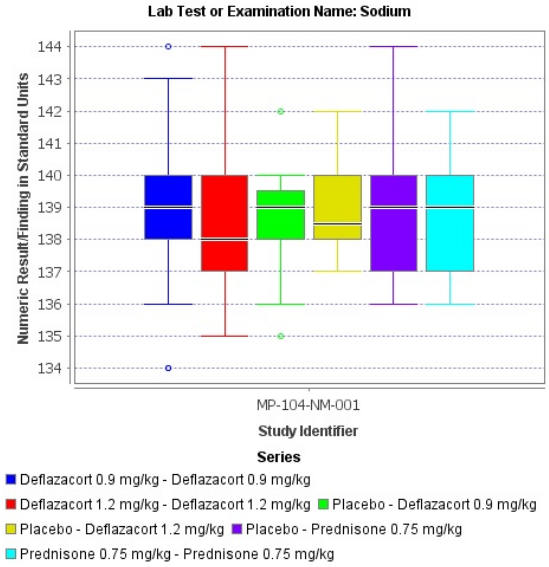


Figure 21: Chloride: Whiskers plot with outliers (Normal range 95-105 mmol/L)

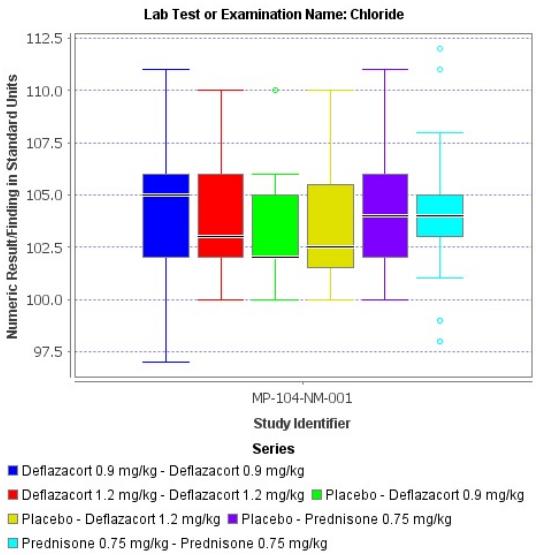


Figure 22: Potassium: Whiskers plot with outliers (Normal range 3.5-5 mmol/L)

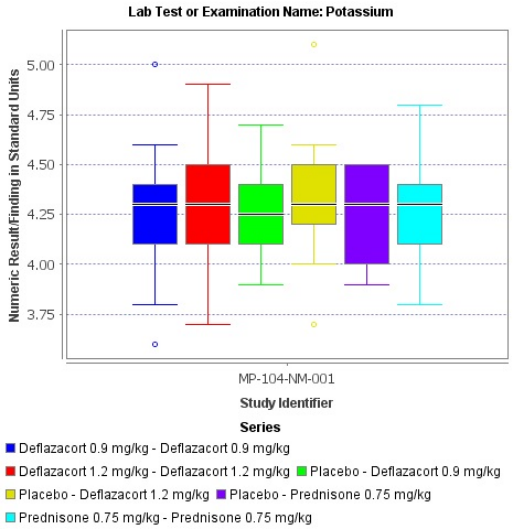


Figure 23: Phosphate: Whiskers plot with outliers (Normal range 0.8-1.5 mmol/L)

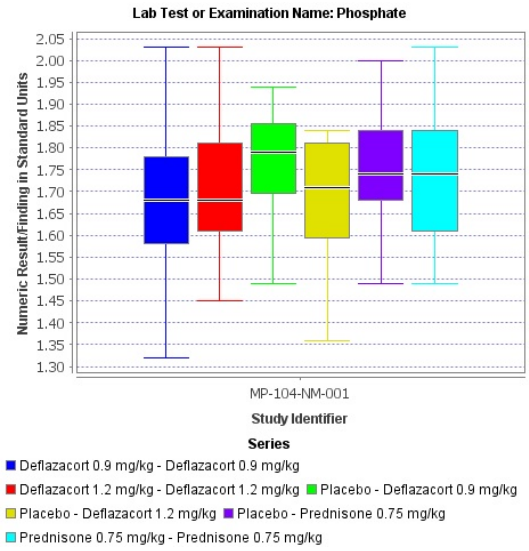


Figure 24: BUN: Whiskers plot with outliers (Normal range 2.5 to 7.1 mmol/L)

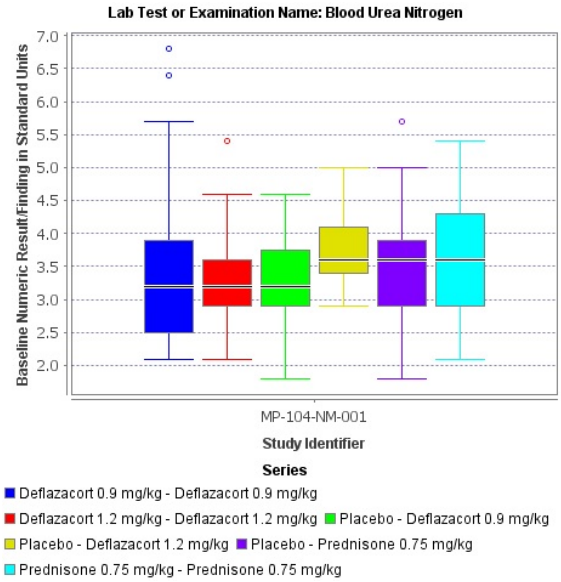
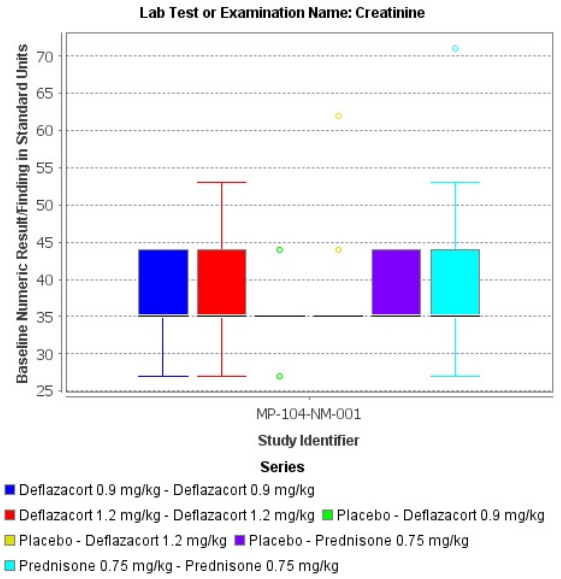


Figure 25: Creatinine: Whiskers plot with outliers (Normal range 50-110 µmol/L)



8.4.7. Vital Signs

Height

As described by the applicant, height percentiles showed a mean decrease at months 3, 6, and 12 for the total deflazacort group (-2.82%, -3.06%, and -11.75%, respectively). "In the placebo group, a slight mean decrease in height percentile was observed at Month 3 (-0.21%), and mean increases were observed at Month 6 (3.99%) and Month 12 (4.28%). It is noted that there were few subjects in the placebo group at Month 6 and Month 12, as most placebo subjects were from Study MP-104-NM-001 and only had laboratory data through Month 3" (ISS, p. 216).

Weight

The applicant also reports that weight percentiles increased more for the total deflazacort group at months 3, 6, and 12 (2.77%, 4.62%, and 6.49%, respectively) than for the placebo group (0.95%, 3.84%, and 2.91%, respectively). Mean increases in the total deflazacort group were greater than mean increases observed for the placebo group. Regarding body mass index (BMI), the applicant reports that "the mean increases were greater at all time points in the total deflazacort group (0.675, 0.990, and 1.959 kg/m2, respectively) compared with the placebo group (0.104, 0.370, and 0.647 kg/m2, respectively)" (ISS, p. 223).

Blood Pressure

The applicant reports that none of the changes from baseline to week 12 of Study NM-001 in vital sign parameters (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature) among treatment groups were clinically significant.

The maximum changes from baseline blood pressures and temperatures for Study MP-104-NM-001 are shown in the following figures. *There does not appear to be a large difference among the treatment groups, although the three outliers with the largest increase in systolic blood pressure from baseline were in the deflazacort 1.2mg/kg group.* Only one deflazacort-treated patient had a systolic blood pressure greater than 140 mm Hg. Subject 159 in the 1.2mg/kg deflazacort arm of Study MP-104-NM-001 had a blood pressure of 198/50 with heart rate of 115 at week 24, *which classifies as an urgent hypertensive crisis.* No temperature was recorded. His white blood cell count was normal on that date. Adverse events recorded for this patient near the date of this blood pressure reading were cough and Cushingoid appearance. Subjects 084 and 104 in study MP-104-NM-001 had low baseline blood pressures of 88/40 and 70/40, respectively, prior to receiving any study treatment.

Figure 26: Maximum systolic (left) and diastolic (right) blood pressure changes

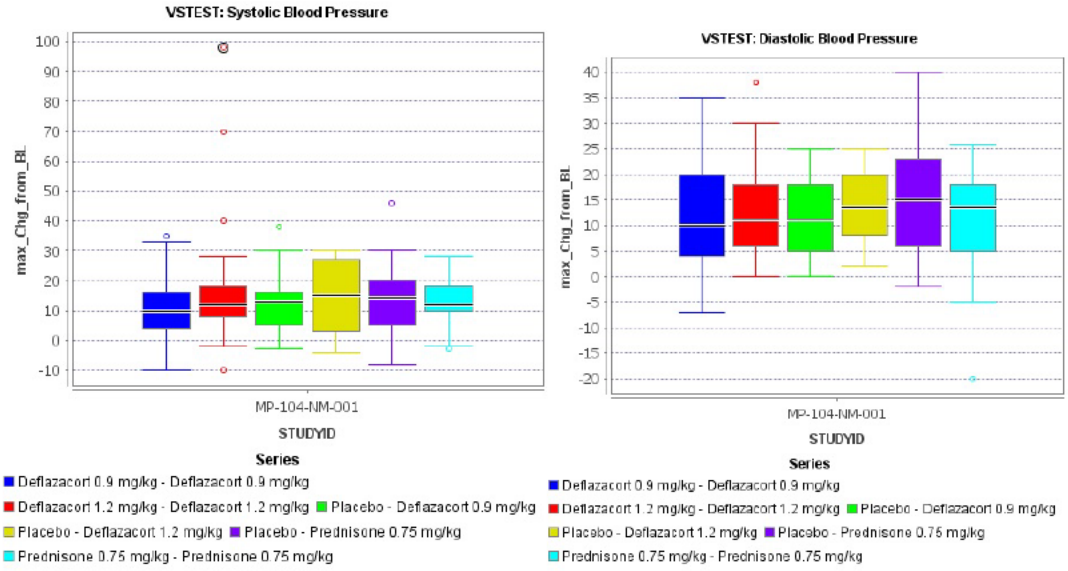
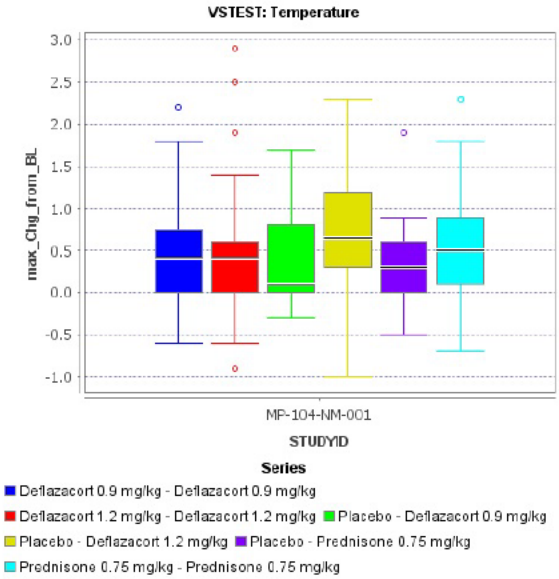


Figure 27: Maximum temperature changes



8.4.8. Electrocardiograms (ECGs)

ECG monitoring was included in the Phase 1 safety studies. The applicant reports "no clinically important trends in the … electrocardiography … assessments" (Summary of Clinical Pharmacology Studies, p. 62). ECG monitoring was also included in the Phase 3 trial MP-104-NM-002 at the beginning and end of the treatment period. Data on ECG assessment were

provided for only 2 patients (NM-002 study report, p. 78). No additional ECG data were available from the applicant.

8.4.9. QT

The NDA contains an argument for why QT studies are not needed based on nonclinical animal data and in vitro hERG assay. There is no evidence of torsade de pointes in the marketing history. Deflazacort clinical trials had no reported AEs of torsade de pointes or other ventricular arrhythmias. There was one case of tachycardia in the Phase 1 studies and two in the Phase 3 studies. There was one reported cardiac arrest in Study MP-104-NM-001 in the setting of emergency appendectomy which does not appear to be related to study drug. ECG monitoring was included in the Phase 1 safety studies and in the Phase 3 Study MP-104-NM-002, but there were no specific QT interval studies. *In this reviewer's opinion, the available clinical evidence from studies and international marketing history suggests minimal risk of cardiac arrhythmogenic potential. A decision regarding the applicant's QT study waiver request will be deferred to the QT-IRT reviewer.*

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

In addition to the multiple adverse events known to be associated with corticosteroid use, the following safety issues are of particular relevance due to their potential severity. Note that there were no patients treated with deflazacort who developed glaucoma, liver failure, or gastrointestinal inflammatory conditions in the studies submitted by the applicant. Additional vision-related adverse events are described below under Cataracts.

8.5.1 Cataracts

In placebo-controlled studies, cataracts occurred more frequently in subjects who received deflazacort (4 subjects [2.3%]) than placebo (0). Cataracts are a known adverse effect of corticosteroids. See the figure below copied from the submission.

Figure 28: Vision effects of deflazacort

Incidence of TEAEs of Special Interest – Glaucoma SMQ, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE in the glaucoma SMQ	4 (4.3%)	2 (3.1%)	1 (5.6%)	2 (3.2%)	0 (0.0%)	7 (4.0%)
Cataract	3 (3.2%)	1 (1.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	4 (2.3%)
Eye pain	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.6%)
Facial pain	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Photophobia	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Visual acuity reduced	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

Source: ISS Table 4.2.8.2.
DMD = Duchenne muscular dystrophy; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for coding of AEs.

8.5.2 Psychiatric Complications

In placebo-controlled studies, hostility and aggression occurred more frequently in subjects who received deflazacort than placebo. Emotional lability is a known adverse effect of corticosteroids. See the figure below copied from the submission.

Figure 29: Psychiatric adverse events

Incidence of TEAEs of Special Interest – Hostility/Aggression SMQ, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE in the hostility/aggression SMQ	26 (28.0%)	11 (16.9%)	1 (5.6%)	16 (25.4%)	7 (11.5%)	38 (21.6%)
Abnormal behaviour	7 (7.5%)	4 (6.2%)	1 (5.6%)	9 (14.3%)	3 (4.9%)	12 (6.8%)
Irritability	7 (7.5%)	2 (3.1%)	0 (0.0%)	3 (4.8%)	2 (3.3%)	9 (5.1%)
Aggression	5 (5.4%)	2 (3.1%)	0 (0.0%)	5 (7.9%)	1 (1.6%)	7 (4.0%)
Psychomotor hyperactivity	5 (5.4%)	2 (3.1%)	0 (0.0%)	3 (4.8%)	1 (1.6%)	7 (4.0%)
Affect lability	4 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.3%)
Laceration	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.6%)
Mania	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Substance-induced psychotic disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

Source: ISS Table 4.2.8.4.
DMD = Duchenne muscular dystrophy; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for coding of AEs.

8.5.3 Hypertension

In placebo-controlled studies, elevated blood pressure (hypertension) occurred more frequently in subjects who received deflazacort than placebo. In the studies submitted for this

application, one DMD patient receiving deflazacort 1.2mg/kg had a potentially dangerous blood pressure elevation to 198/50, discussed above in Section 8.4.7. Blood pressure elevation is a known adverse effect of corticosteroids. See the figure below copied from the submission.

Figure 30: Hypertension

Incidence of TEAEs of Special Interest – Hypertension SMQ, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE in the hypertension SMQ	0 (0.0%)	1 (1.5%)	0 (0.0%)	2 (3.2%)	0 (0.0%)	1 (0.6%)
Blood pressure increased	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.6%)
Hypertension	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.6%)

Source: ISS Table 4.2.8.5.
DMD = Duchenne muscular dystrophy; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for coding of AEs.

8.5.4 Osteoporosis

In placebo-controlled studies, osteoporosis/osteopenia occurred more frequently in subjects who received deflazacort than placebo. Osteoporosis is a known adverse effect of corticosteroids. See the figure below copied from the submission.

Figure 31: Osteoporosis

Incidence of TEAEs of Special Interest – Osteoporosis/Osteopenia SMQ, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE in the osteoporosis/osteopenia SMQ	2 (2.2%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	5 (2.8%)
Osteopenia	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	3 (1.7%)
Bone density decreased	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Femur fracture	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Osteoporosis	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Spinal fracture	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)

Source: ISS Table 4.2.8.7.
DMD = Duchenne muscular dystrophy; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for coding of AEs.

8.5.5 Metabolic and Nutritional

In placebo-controlled studies, metabolic and nutritional adverse events occurred more frequently in subjects who received deflazacort than placebo. In the submitted studies, both

weight and body mass index (BMI) increased more in the deflazacort groups than in placebo. See Section 8.4.7 for details. These adverse effects are known to be associated with corticosteroid use. See the figure below copied from the submission.

Figure 32: Metabolic and nutritional adverse events

Incidence of TEAEs of Special Interest – Hyperglycemia/New Onset Diabetes Mellitus SMQ, DMD Patients

Preferred Term	Deflazacort 0.9 mg/kg/day (N = 93)	Deflazacort 1.2 mg/kg/day (N = 65)	Deflazacort 2 mg/kg Alternate Days (N = 18)	Prednisone 0.75 mg/kg/day (N = 63)	Placebo (N = 61)	Total Deflazacort (N = 176)
Number of subjects with at least 1 TEAE in the hyperglycaemia/new onset diabetes mellitus SMQ	37 (39.8%)	34 (52.3%)	4 (22.2%)	38 (60.3%)	8 (13.1%)	75 (42.6%)
Weight increased	21 (22.6%)	20 (30.8%)	1 (5.6%)	22 (34.9%)	3 (4.9%)	42 (23.9%)
Central obesity	17 (18.3%)	16 (24.6%)	0 (0.0%)	27 (42.9%)	2 (3.3%)	33 (18.8%)
Increased appetite	11 (11.8%)	8 (12.3%)	2 (11.1%)	12 (19.0%)	1 (1.6%)	21 (11.9%)
Polyuria	2 (2.2%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	3 (1.7%)
Weight decreased	2 (2.2%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	3 (1.7%)
Thirst	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)
Coma	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Glucose urine present	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Obesity	1 (1.1%)	0 (0.0%)	0 (0.0%)	2 (3.2%)	0 (0.0%)	1 (0.6%)

Source: ISS Table 4.2.8.8.
DMD = Duchenne muscular dystrophy; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: percentages are n/N x 100. At each level of summarization, a subject is only counted once. MedDRA version 17.0 was used for coding of AEs.

8.6. Safety Analyses by Demographic Subgroups

Reviewer Comment: Note that there is generally no race/ethnic/gender-specific dosing for corticosteroids.

The placebo-controlled studies included only males because DMD is an x-linked recessive disease and female manifesting carriers are very rare. The studies were largely limited to whites/Caucasians. The age range was limited to the pediatric population (ages 5-15 years). It is therefore not possible to conduct analyses of safety information for demographic interactions of age, sex, or racial and ethnic subgroups. Demographics of the placebo-controlled studies are described in the figures below. No demographics data were available for Study MP-104-NM-002.

Figure 33: Age statistics for Study MP-104-NM-001

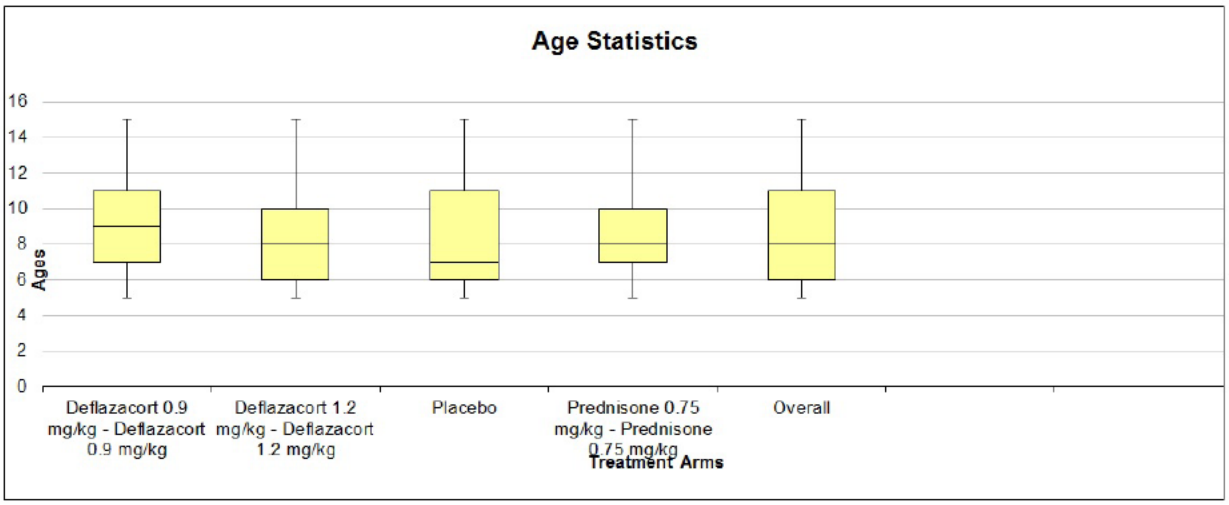


Figure 34: Demographics of Study MP-104-NM-001

Demographic Baseline Characteristics: Race

NDA/BLA: 208684&208685
Study: mp-104-nm-001
Analysis run date: 2016-07-26 10:37:29 AM

Race	Deflazacort 0.9 mg/kg - Deflazacort 0.9 mg/kg N=51		Deflazacort 1.2 mg/kg - Deflazacort 1.2 mg/kg N=49		Placebo N=50		Prednisone 0.75 mg/kg - Prednisone 0.75 mg/kg N=46		Overall N=196	
	Count	%	Count	%	Count	%	Count	%	Count	%
ASIAN	0	0.0	1	2.0	0	0.0	0	0.0	1	0.5
WHITE	46	90.2	45	91.8	49	98.0	45	97.8	185	94.4
OTHER	5	9.8	3	6.1	1	2.0	1	2.2	10	5.1

8.7. Specific Safety Studies/Clinical Trials

Not applicable. No specific study or clinical trial was conducted to evaluate a specific safety concern.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Review of MedDRA SOC for neoplasms found 3 reported cases of "skin papilloma" in the deflazacort group in Study MP-104-NM-001. Skin/cutaneous papillomas are benign skin tags that may be removed if irritated by clothing or for cosmetic reasons.

One adult patient (age 69) being treated with deflazacort for rheumatoid arthritis died of

Kaposi's sarcoma. *The relationship of deflazacort to this death is unclear. Advanced age or corticosteroid-related immunosuppression can lead to Kaposi's sarcoma.*

8.8.2. Human Reproduction and Pregnancy

There were no deflazacort exposures in pregnancies and no exposures in lactating women during the development program. There is a single case-report in the literature (Blanda et al., 1991) about of a twice-pregnant patient with Systemic Lupus Erythematosus who had successful pregnancy with a therapy based on cloroquine first and corticosteroids (deflazacort, methylprednisolone) subsequently.

Adverse developmental outcomes including orofacial clefts (cleft lip with or without cleft palate) and intrauterine growth restriction and decreased birth weight have been reported (Carmichael & Shaw, 1999; Mariotti et al., 2004) with maternal use of corticosteroids during pregnancy. Subsequent studies (Hviid & Mølgaard-Nielsen, 2011; Skuladottir et al., 2014) did not show an increased risk of orofacial clefts with the use of corticosteroids during pregnancy.

8.8.3. Pediatrics and Assessment of Effects on Growth

Corticosteroids are known to cause dose-related growth retardation during human development.

The Phase 3 studies of deflazacort included only pediatric patients (males aged 5-15 years). As described by the applicant and in Section 8.4.7, height percentiles showed a mean decrease at months 3, 6, and 12 for the total deflazacort group (-2.82%, -3.06%, and -11.75%, respectively). "In the placebo group, a slight mean decrease in height percentile was observed at Month 3 (-0.21%), and mean increases were observed at Month 6 (3.99%) and Month 12 (4.28%). It is noted that there were few subjects in the placebo group at Month 6 and Month 12, as most placebo subjects were from Study MP-104-NM-001 and only had laboratory data through Month 3" (ISS, p. 216).

See Section 8.4.7 for a discussion of the effects of deflazacort on weight.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The 50% lethal dose (LD50) for deflazacort is greater than 4000 mg/kg in laboratory animals (Nayak & Acharjya, 2008). There were no reports of overdose in any subject during the clinical trials. The maximum dose used acutely in international deflazacort labels is 1.5mg/kg daily (UK label). Death from overdose is therefore unlikely.

No formal nonclinical or clinical abuse liability studies were conducted in the deflazacort development program.

As described in the ISS (p. 266), "no safety signal has been identified following discontinuation of deflazacort, nor has a withdrawal syndrome associated with deflazacort treatment been observed." Deflazacort is in the class of corticosteroids. *The abrupt cessation of corticosteroids following chronic treatment can lead to potentially fatal adrenal crisis. Deflazacort should therefore be tapered gradually to discontinue treatment after prolonged use. In Study MP-104-NM-001, the deflazacort dose was decreased by a maximum of 5mg every two weeks until withdrawal was complete.*

The drug label for deflazacort (Calcort) in the United Kingdom states that "a 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. This may occur in patients even without evidence of adrenal insufficiency."

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Deflazacort has international approvals for multiple autoimmune conditions and hypersensitivity reactions in the United Kingdom, Switzerland, Spain, Germany, Greece, Italy, Portugal, Mexico, Central & South America, the Caribbean, India, and South Korea.

The following information about undesirable effects is taken from the deflazacort (Calcort) drug label from the United Kingdom (May 17, 2015 revision).

"The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage; timing of administration and the duration of treatment (see Section 4.4).

The following CIOMS frequency rating is used: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).

Endocrine disorders
Uncommon: Suppression of the hypothalamic-pituitary-adrenal axis, amenorrhoea, Cushingoid facies.
Not known: Growth suppression in infancy, childhood and adolescence.

Metabolism and nutrition disorders
Common: Weight gain.
Uncommon: impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, sodium and water retention with hypertension, potassium loss and hypokalaemic alkalosis when coadministered with beta 2-agonist and xanthines.
Not known: Negative protein and calcium balance, increased appetite.

Infections and Infestations
Uncommon: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4).
Not known: candidiasis.

Musculoskeletal and connective tissue disorders
Uncommon: Osteoporosis, vertebral and long bone fractures.
Rare: Muscle wasting
Not known: avascular osteonecrosis, tendonitis and tendon rupture when coadministered with quinolones (see section 4.4), myopathy (acute myopathy may be precipitated by non-depolarising muscle relaxants – see section 4.5), negative nitrogen balance.

Reproductive system and breast disorders
Not known: Menstrual irregularity

Cardiac disorders
Not known: Heart failure

Nervous system disorders
Uncommon: Headache, vertigo.
Not known: restlessness, Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal, aggravation of epilepsy.

Psychiatric disorders
A wide range of psychiatric reactions including affective disorders such as:
Uncommon: depressed and labile mood.
Not known: irritable, euphoric, suicidal thoughts.
Psychotic reactions including:
Not known: mania, delusions, hallucinations, aggravation of schizophrenia
Other reactions including:
Uncommon: behavioural disturbances
Not known: anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported.

Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Eye disorders
Not known: Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts especially in children, chorioretinopathy (see section 4.4), corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Gastrointestinal disorders
Uncommon: Dyspepsia, peptic ulceration, haemorrhage, nausea.
Not known: perforation of peptic ulcer, acute pancreatitis (especially in children), candidiasis.

Skin and subcutaneous tissue disorders
Uncommon: hirsutism, striae, acne,
Rare: bruising
Not known: Skin atrophy, telangiectasia.

General disorders and administration site conditions
Uncommon: Oedema.
Not known: impaired healing.

Immune system disorders
Uncommon: Hypersensitivity including anaphylaxis has been reported.

Blood and lymphatic system disorders
Not known: Leukocytosis

Vascular disorders
Not known: Thromboembolism in particular in patients with underlying conditions associated with increased thrombotic tendency, rare incidence of benign intracranial hypertension"

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable. See Section 8.9.1.

8.10. Additional Safety Issues From Other Disciplines

The reader is referred to Section 4 of this review.

8.11. Integrated Assessment of Safety

The adverse events profile found in the clinical studies of deflazacort is consistent with the adverse events known to be associated with the class of corticosteroids in general. In the primary and supporting clinical studies of deflazacort, the most commonly observed (≥ 10%) adverse events associated with the use of deflazacort 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%) [Source: ISS Table 4.2.1.1.1]. Note that the applicant's 180-day safety update was also reviewed and found to have no new deaths or serious adverse events.

Weight Gain

The most clinically relevant adverse event that caused the most patients to drop out of studies and that may limit DMD patients' use of deflazacort is weight gain. Increased weight could further limit mobility in a patient who is getting weaker due to the underlying disease. The increased risk of bone fractures due to osteopenia could be further compounded by an increased risk of falls in a weakening patient who is getting heavier.

Infection

As with other corticosteroids, patients treated with deflazacort appear to be more susceptible to infectious disease due to immunosuppression, as indicated by the increased rates of upper respiratory tract infections and influenza in the deflazacort arms of the submitted studies. One study patient treated with deflazacort developed a potentially life-threatening encephalitis.

Hypertension

One study patient treated with deflazacort 1.2mg/kg had a hypertensive episode with elevated blood pressure (198/50) that classifies as an urgent hypertensive crisis. Corticosteroids are known to cause elevations in blood pressure.

Psychiatric symptoms

A range of psychiatric adverse events were reported at a greater rate in the deflazacort groups compared to placebo: abnormal behavior (6.8% vs. 4.9% placebo), irritability (5.1% vs. 3.3% placebo), aggression (4% vs. 1.6% placebo), psychomotor hyperactivity (4% vs. 1.6% placebo), affect lability (2.3% vs. 0% placebo), and mania (0.6% vs. 0% placebo). The potential for more serious psychiatric adverse events exists given the relatively small numbers of deflazacort-

treated patients studied and based on the known adverse events in the class of corticosteroids. One study patient treated with deflazacort developed psychotic symptoms, although they may have been due to an underlying encephalitis (which itself could have been precipitated by steroid-induced immunosuppression).

Other potentially serious adverse events
Other potentially life-threatening adverse events, not seen in the submitted clinical studies but reported in the literature, are toxic epidermal necrolysis (6 reported cases) and Stevens-Johnson Syndrome (1 reported case). See Section 8.4.2 for details. Given the multiple countries in which deflazacort has been in use for more than a decade, these severe adverse events appear to be rare and without a known incidence rate.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Labeling Recommendations

10.1. Prescribing Information

This reviewer has the following comments for the deflazacort label.

1. Patients should have regular monitoring of blood pressure and serum levels of sodium and potassium during treatment.
2. Deflazacort should be tapered gradually after chronic use. There are no evidence-based guidelines for when a steroid can be stopped abruptly versus tapered.
3. Toxic epidermal necrolysis and Stevens-Johnson syndrome are possible life-threatening SAEs of deflazacort reported in the medical literature that should be included in the deflazacort label. See Section 8.4.2 for analysis and discussion.

10.2. Patient Labeling

Not applicable.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable to this review.

12 Postmarketing Requirements and Commitments

This section is not applicable to this review.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NM-001 and NM-002

Was a list of clinical investigators provided:	Yes x☐	No ☐ (Request list from applicant)
Total number of investigators identified: 5 with available financial information; 9 without		

<table>
<tr><td colspan="3">available financial information due to age of the study (from 1980s & 1990s).</td></tr>
<tr><td colspan="3">Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 0

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator: 0

Sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes x☐</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes x☐</td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes x☐</td><td>No ☐ (Request explanation from applicant)</td></tr>
</table>

13.3. Table of All Studies. Source: Synopsis of Individual Studies, pp. 1-9

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MP-104-CL-023	Module 5	Determine the effect of hepatic impairment on the pharmacokinetics (PK) of the active deflazacort metabolite, 21 des-DFZ in subjects with moderate hepatic impairment.	Phase 1, multicenter, nonrandomized, open label, single dose	Total dose of 36 mg of deflazacort (6 x 6 mg oral tablets) Single dose	16	Healthy subjects (8 healthy subjects, 8 subjects with moderate hepatic impairment)	1 day	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MP-104-CL-024	Module 5	Determine the effect of renal impairment on the pharmacokinetics (PK) of the active deflazacort metabolite, 21 des-DFZ in subjects with end-stage-renal disease (ESRD).	Phase 1, multicenter, nonrandomized, open label, single dose	Total dose of 36 mg of deflazacort (6 x 6 mg oral deflazacort tablets) Single dose	16	Healthy subjects (8 healthy subjects, 8 subjects with ESRD)	1 day	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MP-104-CL-025	Module 5	Determine the potential effects of multiple doses of rifampin or clarithromycin on the single dose pharmacokinetics (PK) of the deflazacort active metabolite (21 des-DFZ) in healthy adult subjects.	Phase 1, single center, open label, parallel design, single-dose, with 2 fixed sequences	**Cohort A** Period 1: Single dose of 18 mg of deflazacort (3 x 6 mg oral tablets) Period 2: Rifampin 600 mg (2 x 300 mg capsules) QD for 10 days with a single dose of 18 mg of deflazacort (3 x 6 mg oral tablets) coadministered on Day 10 **Cohort B** Period 1: Single dose of 18 mg of deflazacort (3 x 6 mg oral tablets) Period 2: Clarithromycin 500 mg (1 x 500 mg tablet) BID for 10 days with a single dose of 18 mg of deflazacort (3 x 6 mg oral tablets) coadministered on Day 10	28	Healthy Subjects	1 day for Period 1 of each cohort, 10 days for Period 2 of each cohort (10 days of rifampin or clarithro-mycin, 1 day of deflazacort)	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE/ Food Effect	MP-104-CL-026	Module 5	Assess the comparative bioavailability and food effect of deflazacort	Phase 1, single center, open label, randomized, single dose, 5 period crossover	**Dosing sequence A:** Deflazacort 36 mg oral tablet, fasted **Dosing sequence B:** Deflazacort 36 mg oral tablet, high fat meal **Dosing sequence C:** Deflazacort 36 mg crushed oral tablet in applesauce, fasted **Dosing sequence D:** Deflazacort investigational formulation tablets 6 x 6 mg oral tablets, fasted **Dosing sequence E:** Deflazacort 36 mg oral suspension in apple juice, fasted	45	Healthy Subjects	1 day in each of the 5 study periods	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BEA	MP-104-CL-058	Module 5	Assess the relative bioavailability of 21-desDFZ after oral administration of Marathon's commercial formulation of deflazacort (MP-104) 36 mg (1 × 36 mg) tablet compared to the current marketed, Calcort® formulation of deflazacort 36 mg (6 × 6 mg) tablets in healthy volunteer subjects. Assess the safety of Marathon's commercial formulation of deflazacort (MP-104) when administered as a single 36 mg dose. Characterize the pharmacokinetics of 21-desDFZ and 6-β-OH-21-desDFZ	Phase 1, single center, open label, randomized, single dose, 2 period crossover	Dosing sequence A: Deflazacort 36 mg oral tablet Dosing sequence B: Calcort® 6mg x 6 oral tablets	50	Healthy subjects	1 day in each of the 2 study periods	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MP-104-CL-005	Module 5	Descriptively characterize the single-dose and steady-state PK of deflazacort (if measurable) and 21-desacetyldeflazacort after oral administration of deflazacort at the therapeutic dose (0.9 mg/kg/day) in DMD subjects and to assess the safety and tolerability of single-dose and steady-state deflazacort.	Phase 1, multicenter, nonrandomized, open label.	Day 1 (CRU): 0.9 mg/kg deflazacort (between 2 to 12 × 6 mg oral tablets based on body weight) Day 2-7 (home): 0.9 mg/kg deflazacort (2 to 12 × 6 mg oral tablets) QD (+ 2 days) Day 8 (CRU): 0.9 mg/kg deflazacort (2 to 12 × 6 mg oral tablets)	24	Patients with DMD	8 days	Completed; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	MP-104-CL-022OLE	Not applicable	Assess the safety and tolerability of long-term use of deflazacort in DMD subjects that were previously enrolled in the MP-104-CL-005 PK study.	Phase 3, multicenter, open label, extension study	Deflazacort 0.9 mg/kg QD, oral tablets	25	Patients with DMD	Up to 16 months (up to commercial availability)	Ongoing; none
Safety	MP-104-CL-037	Not applicable	Expanded access program, where deflazacort is supplied free of charge and shipped directly to patients or parent(s)/ legal guardian(s), as appropriate.	Phase 3, open-label	Deflazacort 6, 18, 30, and 36 mg tablets, oral solution	Up to 1500	Patients with DMD	Up to16 months (up to commercial availability)	Ongoing; none

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy & Safety	MP-104-NM-001	Module 5	Assess the safety & efficacy of DFZ and prednisone vs placebo at 12 weeks of treatment in improving muscle strength in D/B- MD patients	Phase 3, multicenter, double-blind , randomized, parallel-group, placebo-controlled	Deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for the first 12 weeks of treatment. Deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, or prednisone 0.75 mg/kg/day for the subsequent 40 weeks.	196	Patients with DMD	52 weeks	Completed; Full CSR
Safety	MP-104-NM-057	Not applicable	Compare the long-term (12 to approximatel y 25 months) safety and efficacy of deflazacort to prednisone in D/B-MD patients having previously completed Study MP-104-NM-001	Phase 3, multicenter, double blind, randomized, parallel group follow on study to Study MP-104-NM-001	Deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, or prednisone 0.75 mg/kg/day	Unknown	Patients with DMD	52 weeks	Completed; Not applicable

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy & Safety	MP-104-NM-002	Module 5	Assess the safety & efficacy of deflazacort vs placebo in improving muscle function in patients with DMD	Phase 3, multicenter, double blind, randomized, parallel group, placebo-controlled	Deflazacort 2 mg/kg once every 2 days, oral tablets Placebo once every 2 days, oral tablets	29	Patients with DMD	Up to 2 years	Completed; Full CSR

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/s/

RAINER PAINE
01/17/2017

NICHOLAS A KOZAUER
01/17/2017