# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208684Orig1s000
# 208685Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Review Addendum

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| **NDA Number** | NDA208684 and 208685 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA208684\0000<br>\\CDSESUB1\evsprod\NDA208685\0000 |
| **Submission Date** | 06/09/2016 |
| **Submission Type** | Priority |
| **Brand Name** | EMFLAZA™ |
| **Generic Name** | Deflazacort |
| **Dosage Form and Strength** | Tablets: 6 mg, 18 mg, 30 mg, and 36 mg<br>Suspension: 22.75 mg/mL supplied as 13 mL in a 20 mL bottle |
| **Route of Administration** | Oral |
| **Proposed Indication** | Duchenne Muscular Dystrophy (DMD) |
| **Applicant** | Marathon Pharmaceuticals, LLC |
| **Associated IND** | IND 119258 |
| **OCP Review Team** | Bilal AbuAsal, PhD; Atul Bhattaram , PhD; Kevin Krudys, PhD; Ping Zhao, PhD; Sreedharan Sabarinath, PhD. |
| **OCP Final Signatory** | Mehul Mehta, PhD. |

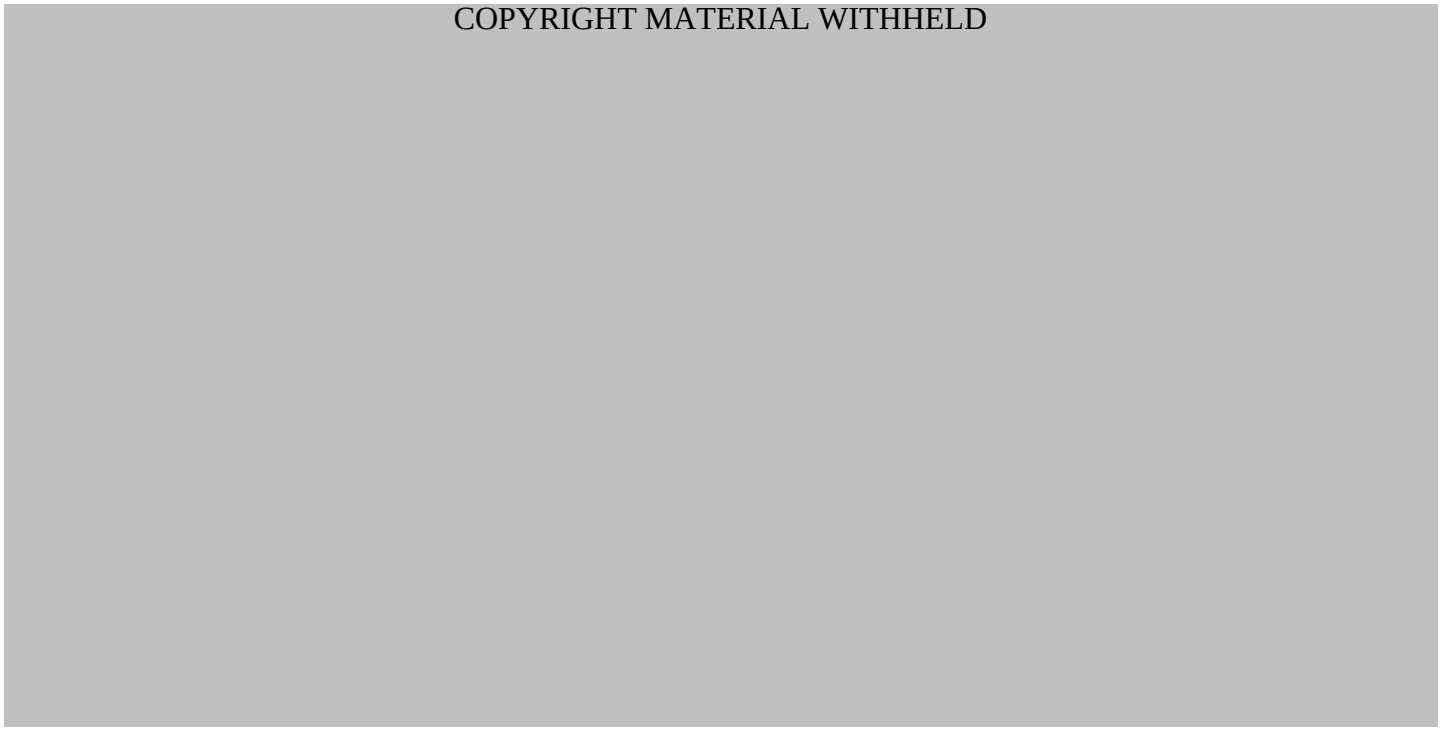
**BACKGROUND**

This is an addendum to the clinical pharmacology review submitted to DARRTS on November 8th 2016. The purpose of this document is to review the metabolic profile of deflazacort and discuss the clinical amendment submitted by the Applicant on 12/13/2016.

**Metabolic Profile of Deflazacort:**

In-vitro metabolism studies showed that deflazacort is rapidly converted by esterase to the active metabolite 21-desacetyl deflazacort (21-desDFZ or Metabolite II). 21-desDFZ, is further metabolized by CYP3A4 to several other metabolites Figure 1.

**Figure 1. Proposed metabolic pathway for 21-desacetyl deflazacort (21-desDFZ).**




Source: Martinelli et al. Drug Metab Dispos. 1979; 7(5):335-339)

Analysis of clinical data following oral administration of radio-labeled deflazacort to healthy subjects (N=3) identified 6β-hydroxy deflazacort (Metabolite III) as a major metabolite, accounting to 27% of the total plasma radioactivity[3]. In addition, the exposure of metabolite III was characterized in study MP-104-CL-005 in patients with DMD (N=24) and the ratio of the exposure of 6β-Hydroxy deflazacort (Metabolite III) relative to the active metabolite 21-desDFZ was about 76 % Table 2. Based on these findings, additional in-vitro DDI studies are needed to evaluate if this metabolite is an inhibitor or inducer of major metabolizing enzymes and transporters. This issue can be addressed post marketing for the following reasons:

1. Deflazacort has been in clinical use for several years and is part of treatment guidelines for DMD[1]

[1] American Academy of Neurology- Practice Guideline Update: Corticosteroid Treatment of Duchenne Muscular Dystrophy: https://www.aan.com/Guidelines/home/GetGuidelineContent/732

2. No new safety issues associated with potential drug interactions were identified from clinical experience with deflazacort[2]

**Table 1. Relative abundance of radio-labeled deflazacort and its metabolites in healthy human subjects (N=3)**

| Deflazacort metabolites | % of Total Plasma Radioactivity in Plasma |
|---|---|
| COPYRIGHT MATERIAL WITHHELD | |

Source: Martinelli et al. Drug Metab Dispos. 1979; 7(5):335-339)

**Table 2. Exposure to metabolite III (Median $AUC_{0-8h}$) in DMD patients**

| Human | Children (0.9 mg/kg) (ng/mL*h) | Adolescents (0.9 mg/kg) (ng/mL*h) | All (1.2 mg/kg) (ng/mL*h) |
|---|---|---|---|
| 21-Des (Metabolite II) | 444 | 630 | 478 |
| 6β-OH (Metabolite III) | 338 | 413 | 364 |
| **Metabolite V/VII (estimated)[1]** | **258 (1.4)[2]** | **366 (1.0)[2]** | **278 (1.3)[2]** |

[1] Metabolite V/VII exposures were based on the % of total radioactivity (25.2%) reported in Martinelli et al., 1979.

[2] Value in parenthesis indicates fold coverage ($AUC_{monkey}/AUC_{human}$) compared to estimated male monkey exposures

Source: Clinical amendment submitted on 12/13/2016

In addition, metabolite V (molecular weight 417) is also suggested to be a major circulating metabolite by Martinelli, el al[3] accounting for about 25% of the circulating radioactivity. However the structure of this metabolite was not adequately characterized and was not measured in the subsequent clinical pharmacology studies. In a clinical amendment submitted on December 19th 2016, after the late cycle meeting (LCM), the applicant stated that, "Metabolite V (reported in Martinelli et al, 1979) represents the same mixture of metabolite isomers referred to as metabolite VII (reported in Assandri et al., 1983). This was based on the similar molecular weight (~417) and MS/MS fragmentation patterns reported in these publications. While it is possible that the

[2] Clinical review submitted to DARTTS on 01/17/2017

[3] Source: Martinelli et al. Drug Metab Dispos. 1979; 7(5):335-339)

impurities in the metabolite V fraction interfered with definitive determination of its structure and may represent a mixture of isomers with a molecular weight of 417, this was not definitively established. Huber and Barbuch (Xenobiotica, 1995) tried to identify and determine the structure of metabolite V and proposed it to be an epoxide metabolite using human urine samples. However there is still uncertainty about the structure and relative abundance of metabolite V.

Based on all of the above reasons, the review team is of the opinion that the metabolite V is not well characterized. Additional analysis of samples stored from the completed clinical pharmacology studies is needed to evaluate if metabolite V is a major circulating metabolite or not.

**CONCLUSION & RECOMMENDATIONS:**

(1) 6β-Hydroxyl deflazacort (Metabolite III) is considered as a major circulating metabolite and represent ≥25% of the active moiety of deflazacort. Therefore additional in-vitro studies are needed to evaluate whether this metabolite is an inhibitor or inducer of major metabolizing enzymes and transporters. The following PMR study (in vitro) will be issued to address this issue:

PMR-1: Characterize the potential for CYP and transporter-mediated interactions due to inhibition or induction of these enzymes and transporters in vitro by the 6β-OH-metabolite (Metabolite III) of deflazacort. Refer to the clinical pharmacology drug interaction guidance for in vitro study design considerations:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

(2) There is uncertainty related to the structure and relative abundance of metabolite V in humans. The review team believes that the issue can be addressed with a PMR study to identify and quantify the major metabolites of deflazacort using stored plasma samples from clinical pharmacology studies, if available.

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

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# Office of Clinical Pharmacology Review

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|---|---|
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| **Link to EDR** | \\CDSESUB1\evsprod\NDA208684\0000<br>\\CDSESUB1\evsprod\NDA208685\0000 |
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| **Submission Type** | Priority |
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| **OCP Final Signatory** | Mehul Mehta, PhD. |

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# 1. EXECUTIVE SUMMARY

Deflazacort is a glucocorticoid used as an anti-inflammatory and immunosuppressive agent and is believed to increase muscle strength in patients with Duchenne Muscular Dystrophy (DMD). DMD is a recessive X-linked form of muscular dystrophy that results in muscle degeneration, loss of independent ambulation, impaired pulmonary function, cardio-myopathy and eventually leads to death. The incidence is approximately 1 in 3,500 live male births. Deflazacort is a pro-drug that is metabolized rapidly in plasma by esterases to the active moiety 21-desacetyl deflazacort (21-desDFZ). Deflazacort is not approved in the US but is available in the rest of the world for many approved uses, not including DMD.

The applicant, Marathon Pharmaceuticals LLC, is seeking approval for deflazacort (EMFLAZA™) oral tablets (NDA208684) and oral suspension (NDA208685) for the treatment of DMD. EMFLAZA™ will be available as 6, 18, 30, 36 mg immediate-release tablets and as a 22.75 mg/ml oral suspension.

The applicant is relying on two randomized, double-blind, placebo- and active-controlled studies conducted in patients with DMD conducted in early nineties as the basis for approval. The first study (MP- 104-NM-001) serves as the pivotal study to establish the effectiveness of deflazacort. This study included two doses of deflazacort (0.9 and 1.2 mg/kg/day), one dose of prednisone (0.75 mg/kg/day) and placebo in a once daily regimen. Both doses of deflazacort were found to be effective compared to placebo, but the 1.2 mg/kg/day dose showed relatively higher number of adverse events (AEs). The second clinical study (MP-104-NM-002) included 2 mg/kg/day dose of deflazacort and placebo administered as once in every other day regimen and is considered as supportive evidence for this application.

Deflazacort has been used as standard of care for DMD in Europe and is used by patients in USA as well. The efficacy studies were conducted in the early 1990s, and a direct bridging of the to-be-marketed formulation (EMFLAZA™ tablets) to the clinical trial formulation was not feasible. Therefore, the totality of evidence from the PK exposures obtained from different formulations of deflazacort, various dosing regimens used in the efficacy studies, and the potential impact of formulations on gastrointestinal absorption based on the physicochemical properties of deflazacort were assessed to support the formulation bridging. To support the approval of oral suspension (NDA208685), a pivotal bioequivalence study was conducted to bridge it to EMFLAZA™ tablets.

The applicant also conducted intrinsic (renal/hepatic impairment) and extrinsic factor (effect of food and drug-drug interaction) studies to support dose adjustment recommendations. Population PK analysis, including data from healthy subjects and DMD patients, was conducted to quantify the effect of age, gender, body weight and race on pharmacokinetics of deflazacort.

The primary objectives of this review are: (1) to evaluate the adequacy of the bridging of the clinical trial formulation to the to-be marketed formulation (2) to compare the proposed flat dosing with the (b) (4) body weight adjusted dosing, and (3) to evaluate the dose adjustment recommendations with CYP3A4 inhibitors and inducers.

## 1.1 Recommendations

The Office of Clinical Pharmacology reviewed NDAs 208684 & 208685 and recommends approval. The essential review focus with specific recommendations and comments are summarized below.

| | |
|---|---|
| **Primary evidence of effectiveness:** | Primary evidence of effectiveness was established from two efficacy studies MP-104-NM-001 (pivotal) and MP-104-NM-002 (supportive) in DMD patients aged 5-15 years. In the pivotal study (104-NM-001) efficacy was established based on improvement in average muscle strength score from baseline to week-12 using an 11-point modified version of the Medical Research Council (MRC) index. |
| **General dosing instructions:** | The proposed dose is 0.9 mg/kg once daily in patients with DMD (5 (b) (4) years of age) (b) (4) |
| **Dosing in patient subgroups (intrinsic and extrinsic factors):** | The dosing in patient subgroups (b) (4)<br>• A 3-fold dose reduction of deflazacort for patients concomitantly taking moderate or strong CYP3A4 inhibitors (*i.e.*, a 36 mg regular dose should be reduced to 12 mg with moderate/strong CYP3A4 inhibitors).<br>• Avoid use with moderate or strong CYP3A4 inducers.<br>• Patients with severe hepatic impairment (Child-Pugh C Class) were not studied and no dosing recommendations can be made for severe hepatic impairment. |
| **Labeling** | The labeling concepts are in general adequate (b) (4) |
| **Bridge between the "to-be-marketed" and clinical trial formulations:** | A direct PK bridge between the clinical trial formulation and the to-be-marketed tablet formulation was not feasible. Bridging was established based on the totality of evidence as explained in Section 3.3.6.<br>A pivotal BE study provides the bridge between oral suspension and the to-be-marketed tablets. |

## 1.2 Post-Marketing Requirements and Commitments

None.

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology and Clinical Pharmacokinetics

**Mechanism of Action:** Deflazacort is a pharmacologically inert corticosteroid prodrug that is rapidly converted to its active metabolite, 21-desDFZ. 21-desDFZ exerts its pharmacological effects through the glucocorticoid receptors. It also has anti-inflammatory and immunosuppressant activities. Deflazacort showed increase in muscle strength and function in animal models of DMD.

**Absorption:** Deflazacort is absorbed rapidly and is completely converted by plasma esterases to the pharmacologically active metabolite 21-desDFZ after oral administration. The median $t_{max}$ for tablets taken without food is about 1 hour. Co-administration of tablets with a high-fat meal did not affect the extent of absorption. The administration of deflazacort-crushed tablets in applesauce did not affect its bioavailability. The tablet and suspension formulations of deflazacort are bioequivalent.

**Distribution:** The plasma protein binding of 21-desDFZ is about 40 %.

**Metabolism:** Plasma esterases are responsible for the conversion of deflazacort to its active metabolite, 21-desDFZ. 21-desDFZ is further metabolized by CYP3A4 to inactive moieties.

**Elimination:** The mean terminal elimination half-life of 21-desDFZ ranged from 2 to 3 hours. Majority of the active moiety is eliminated in the urine after metabolism by CYP3A4 as inactive metabolites. Less than 18 % of 21-desFZ was excreted unchanged in the urine.

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

The recommended dosing regimen of deflazacort is 0.9 mg/kg once daily. The dosing was derived from the pivotal trial MP-104-NM-001, which evaluated deflazacort at 0.9 mg/kg/day in comparison to 1.2 mg/kg/day, prednisone as active control and placebo in patients with DMD(N=192). The proposed dose of 0.9 mg/kg/day is effective and the 1.2 mg/kg/day dose was only marginally better, but had relatively increased number of adverse events (AEs).

### *2.2.2 Therapeutic individualization*

**CYP3A4 Inhibitors:** A 3-fold dose reduction is recommended when concomitant use of a moderate or strong CYP3A4 inhibitor is required. In a dedicated drug-drug interaction (DDI) study with multiple doses of clarithromycin, a strong CYP3A4 inhibitor, a 2 to 3 fold increase in $C_{max}$, and $AUC_{inf}$ values of 21-des-DFZ was observed. Physiologically-Based Pharmacokinetic (PBPK) modeling predicted that moderate CYP3A4 inhibitors (e.g. fluconazole) can also increase deflazacort exposure by about 3-fold.

**CYP3A4 Inducers:** The concomitant use of CYP3A4 inducers with deflazacort should be avoided. Based on a DDI study with rifampin, a strong CYP3A4 inducer, the exposure ($C_{max}$ and $AUC_{inf}$) of 21-des-DFZ was approximately 90 % lower following administration of rifampin. PBPK modeling predicted similar effects with moderate CYP3A4 inducers as well.

**Hepatic Impairment:** No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh A and B Class). A dedicated hepatic impairment study was conducted in subjects with moderate hepatic impairment and showed no significant changes in exposure to 21-desDFZ with moderate impairment. There is very limited clinical experience with deflazacort in patients with severe hepatic impairment (Child-Pugh C Class) and therefore no dosing recommendation can be made.

**Renal Impairment:** No dose adjustment is needed for deflazacort by renal function. Based on the results from a dedicated renal impairment study conducted in subjects with end stage renal disease (ESRD, CrCL <15 mL/min, not on the day of dialysis), there was no impact of renal function on the exposure to 21-des-DFZ.

**Age, Gender and Race:** No dose adjustments are needed based on age (5-16 years), sex or race (Caucasian or non-Caucasian). However, deflazacort will be administered on a per kg basis as per the dosing regimen studied in clinical trials and is in agreement with the current treatment guidelines for DMD[1].

## 2.3 Outstanding Issues

The pivotal BE study demonstrated bioequivalence between the to-be-marketed tablets and the oral suspension. However, Office of Study Integrity and Surveillance (OSIS) inspection report for this study is currently pending.

## 2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following recommendations for general dosing and dose adjustment criteria based on intrinsic and extrinsic factors.

- The initially proposed dosing for general population (0.9 mg/kg/day) is acceptable. (b) (4)
- We agree that no dose adjustment is needed in patients with mild and moderate hepatic impairment (Child-Pugh B & C Class) or for patients with any degree of renal function impairment.
- Section 8 of the label should state that there is no clinical experience for dosing in patients with severe hepatic impairment (Child-Pugh C Class) and as a result, a dosing recommendation cannot be provided.
- We agree that dose of deflazacort should be reduced to one third with concomitant administration of strong or moderate CYP3A4 inhibitors (i.e., a regular dose of 36

[1] American Academy of Neurology- Practice Guideline Update: Corticosteroid Treatment of Duchenne Muscular Dystrophy: https://www.aan.com/Guidelines/home/GetGuidelineContent/732

mg should be reduced to 12 mg when given with a strong or moderate CYP3A4 inhibitor drug)

- We agree that concomitant administration of deflazacort with strong or moderate CYP3A4 inducers should be avoided.
- We agree that sex and race (Caucasian vs. non-Caucasians) have no effect on the pharmacokinetics of 21-desDFZ. We recommend that the observed differences in 21-des DFZ exposure between younger (≤12 years) and older (>12 years) DMD patients be included in Section 12.3.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Overview of the Product and Regulatory Background

The NDA 208684 for deflazacort includes a pivotal efficacy study and a smaller supportive study, both conducted in the 1990s. The applicant obtained exclusively licensed data for these two studies to support this application. The applicant is seeking approval for immediate release tablets and a suspension formulation of deflazacort at a dose of 0.9 mg/kg/day. The submission includes 8 clinical and clinical pharmacology studies as well as several *in vitro* studies to inform the labeling. The NDA received priority review status and the PDUFA date is 9th February 2017.

Deflazacort is not approved for any indication in the US; however, it is approved in many other countries for a wide range of conditions that are responsive to glucocorticoids. Even though deflazacort and prednisone, are not approved for the treatment of DMD, both the American Academy of Neurology (AAN) and the Centers for Disease Control (CDC) guidelines recommend glucocorticoids as first-line therapy to improve muscle strength and function in DMD.

## 3.2 General Pharmacological and Pharmacokinetic Characteristics

| **Pharmacology** | |
|---|---|
| **Mechanism of Action** | Deflazacort is a glucocorticoid prodrug with anti-inflammatory and immunosuppressive properties. The potency of deflazacort is believed to be about 75 % of prednisone. |
| **Active Moieties** | 21-desDFZ is the active moiety of deflazacort that is formed rapidly by plasma esterase. 21-desDFZ acts through the glucocorticoid receptors. |
| **QT Prolongation** | The applicant has submitted a TQT study waiver request because no ECG abnormalities were observed in clinical practice. |
| **General Information** | |
| **Bioanalysis** | 21-desDFZ was measured using validated LC/MS/MS methods. A summary of the method validation report is included in |

| | | |
|---|---|---|
| | Appendix 4.1. | |
| **Healthy Volunteers vs. Patients** | Variability in 21-desDFZ exposure is higher in DMD patients (5-15 years of age) compared to adult healthy volunteers. This could be due to the changes in muscle integrity with disease progression in DMD patients. | |
| **Dose Proportionality** | 21-desDFZ exposure increases in a dose proportional manner over a dose range of 3 to 36 mg. | |
| **Accumulation** | No accumulation of 21-desDFZ was observed at steady state with once daily dosing. | |
| **Variability** | Variability (%CV) in $C_{max}$ values was larger in children (96%) compared to adolescents (38%). Consistent with $C_{max}$, the variability in AUC (%CV) was larger in children (85%) than in adolescents (57%). This could be due to changes in muscle integrity with disease progression in DMD patients. | |
| **Absorption** | | |
| **Bioavailability** | The absolute bioavailability of deflazacort has not been determined. A mass balance study showed that the fraction of deflazacort absorbed after oral administration is at least 70%. | |
| **$T_{max}$** | 0.25-2 hrs for the tablets and suspension formulations | |
| **Food effect (high-fat meal) GMR (90% CI) relative to fasted state for tablets** | $AUC_{0-24}$ | $C_{max}$ |
| | 111% (107-116) | 72% (65-79) |
| **Distribution** | | |
| **Volume of Distribution** | Around 15 L based on population PK analysis | |
| **Plasma Protein Binding** | About 40 % | |
| **Blood to Plasma Ratio** | 2.4 for 21-desDFZ | |
| **Substrate transporter systems** | Based on in vitro studies, both deflazacort and 21-desDFZ are substrates for P-gP | |
| **Elimination** | | |
| **Mean Terminal** | 2-3 hours for 21-desDFZ | |

| | |
|---|---|
| **Elimination half-life** | |
| **Metabolism** | |
| **Primary metabolic pathway(s) [*in vitro*]** | Deflazacort is extensively and rapidly metabolized by plasma esterases to the active metabolite 21-desDFZ. 21-desDFZ is mainly metabolized by CYP3A4 to five inactive metabolites. |
| **Inhibitor/Inducer** | Deflazacort and 21-desDFZ are not inhibitor or inducer for any of the major CYP enzymes or transporters. |
| **Excretion** | |
| **Primary excretion pathways** | About 70 % of radio-labeled dose was recovered in the urine. Less than 18 % is excreted as 21-desDFZ. |

## 3.3 Clinical Pharmacology Questions

### *3.3.1 To what extent does the clinical pharmacology information provide supportive evidence of effectiveness?*

Evidence of effectiveness was established from the pivotal efficacy study MP-104-NM-001 and the additional supportive study MP-104-NM-002 in DMD patients.

The pivotal study MP-104-NM-001 was a double-blind, randomized, placebo-and active-controlled, multicenter study to evaluate the safety and efficacy of deflazacort, for improving muscle strength in boys with DMD aged 5 to 15 years (n=196). This study was conducted at 9 centers in the United States and Canada between 1993 and 1995. Patients were randomly assigned to receive treatment with deflazacort 0.9 mg/kg/day, or 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo. The applicant reported a statistically significant improvement in muscle strength compared to placebo for both doses of deflazacort (Figure 1).

The supportive study MP-104-NM-002 was a double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of deflazacort in improving muscle strength in ambulatory male patients with DMD aged 5 to 11 years of age (n=38). This study was conducted at 5 centers in Italy between 1988 and 1991. Patients received deflazacort (2 mg/kg once every 2 days) or placebo in a 2:1 ratio (deflazacort: placebo). In patients treated with deflazacort, an increase in muscle strength was observed at Month 6 (LS mean change from Baseline: 0.57), compared with a decrease in average muscle strength in the placebo group (LS mean change from Baseline (-6.40, p= 0.019). Please refer to Dr. Rainer Paine's clinical review and Dr. Xiang Ling's statistical review for details.

There is no exposure response analysis that provides additional support to the effectiveness of deflazacort.

### *3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?*

(b) (4)

In the pivotal efficacy study, two doses of deflazacort (0.9 and 1.2 mg/kg/day) were compared to placebo for 12 weeks. The Figure 1 below shows the change from baseline in muscle strength at week 12 for the proposed dose of 0.9 mg/kg/day in comparison to 1.2 mg/kg/day dose and placebo in patients with DMD. These results suggest that the initially proposed dose of 0.9 mg/kg/day is effective relative to placebo. The 1.2 mg/kg/day dose was marginally better than the 0.9 mg/kg/day dose for efficacy but the treatment emergent AEs for the 1.2 mg/kg/day group (24/65 patients, 36.9%) was higher than that for the 0.9 mg/kg/day group (17/68 patients, 25.0%). Please refer to the clinical safety review for additional details.

(b) (4)

**Figure 1: Change From Baseline to Week 12 (±SE) in Average Muscle Strength Score in DMD Patients (Pivotal Efficacy Study MP-104-NM-001).**


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### *3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?*

Alternative dosing regimen and management strategy is not required based on age, sex and race. Refer to Section '4.8 Population PK Analysis' for a detailed discussion.

While safety and efficacy of deflazacort have not been established in pediatric patients less than 5 years of age, the PK of 21-desDFZ is not expected to be any different for children older than two years. This is because 21-desDFZ, the active moiety, is mainly metabolized by CYP3A4 and CYP3A4 enzyme is expected to reach maturation by the age of two years. The prodrug deflazacort is converted to the active moiety 21-desDFZ by plasma esterases and is not expected to be any different in children of 2-5 year age group relative to children > 5 years of age.

It is also noted that the PK of deflazacort/21-desDFZ do not appear to be influenced by age or body weight (Section 4.8). However, deflazacort was dosed in a per kg basis in controlled clinical studies that demonstrated efficacy. Current treatment guidelines for DMD also recommend dosing based on body weight. Based on allometric principles, a slight decrease in the plasma concentration in children with lower body weight may be observed with the body weight based dosing regimen.

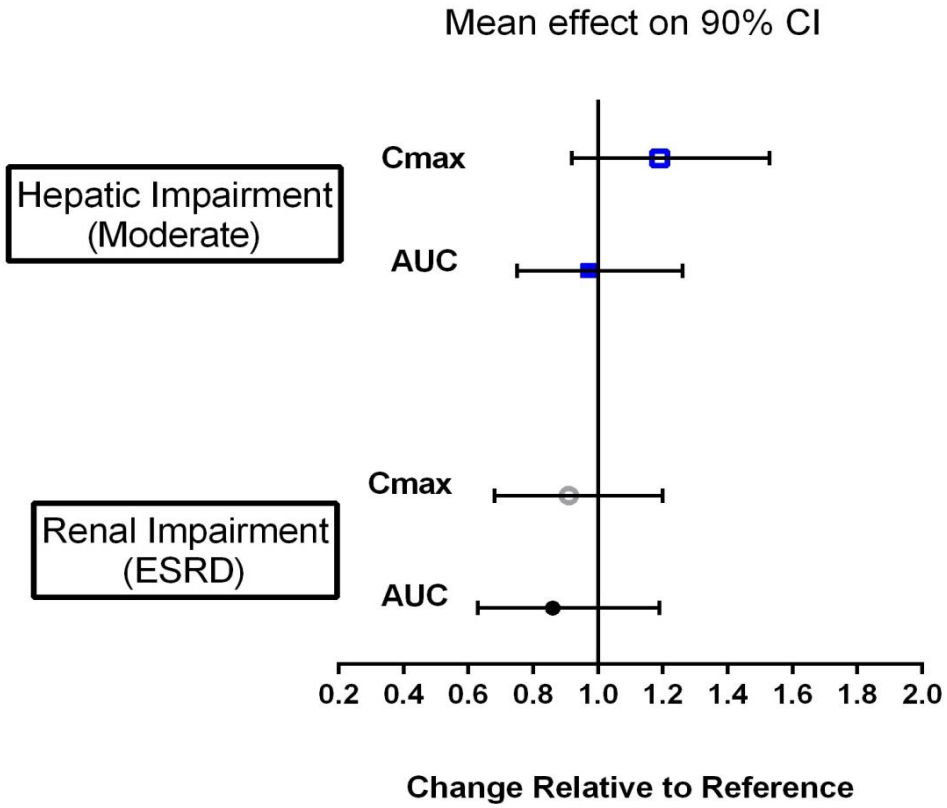
The effect of hepatic and renal impairment on 21-des DFZ were evaluated in dedicated renal and hepatic impairment studies as explained below.

**Renal Impairment:** The effect of renal impairment on the exposure of 21-desDFZ was evaluated in a dedicated renal impairment study (MP-104-CL-024) at 36 mg oral dose level of deflazacort, in 8 subjects with ESRD (Creatinine Clearance less than 15 mL/min, dosed

not on the dialysis day) and 8 healthy control subjects. There was no significant change in exposure in subjects with ESRD relative to healthy controls (Figure 2). Therefore no dose adjustment is needed for patients with any degree of renal impairment.

**Hepatic Impairment:** A dedicated study in subjects with moderate hepatic impairment (Child-Pugh B Class) (N=8) and heathy control subjects (N=8) assessed the effect of hepatic impairment on the exposure of 21-desDFZ after single 36 mg dose administration in fasted condition. There was no clinically significant change in $C_{max}$ and AUC of 21-desDFZ in subjects with moderate hepatic impairment compared to healthy controls. Therefore, no dosing adjustment is recommended in patients with mild and moderate hepatic impairment (Figure 2). The effect of severe hepatic impairment was not studied and there is very limited clinical experience in this patient population to provide specific dosing recommendations.

**Figure 2 Effect of Renal (N=16) and Hepatic (N=16) Impairment on the Pharmacokinetics of 21-desDFZ, the active moiety of deflazacort after Single Dose Administration of Deflazacort (36 mg)**

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### *3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?*

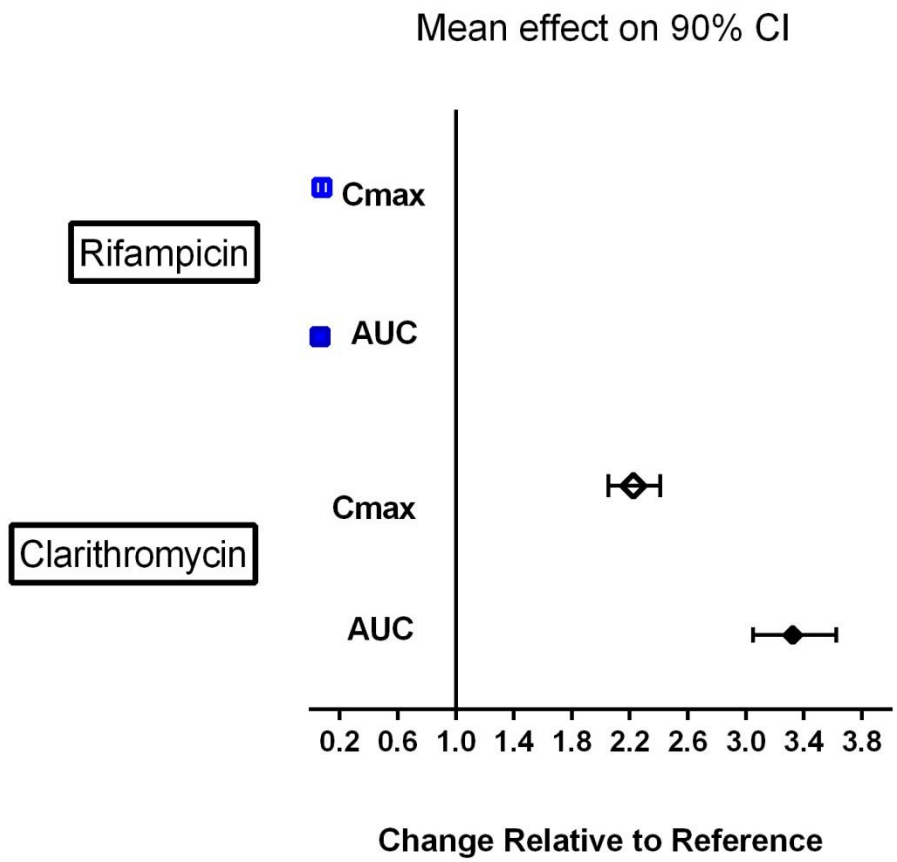
A dose reduction by 3-fold is needed when co-administration with moderate or strong CYP3A4 inhibitors is desired. The use of CYP3A4 inducers should be avoided with deflazacort.

There is no significant food effect with EMFLAZA™ and can be taken without regard to food.

**CYP3A4 Mediated Drug-Drug Interaction:**

*In-vitro* studies showed that deflazacort is a CYP3A4 substrate. Consequently, a drug-drug interaction (DDI) study with a strong CYP3A4 inhibitor (500 mg clarithromycin) and a strong inducer (600 mg rifampin) was performed (Study MP-104-CL-025). The results from this DDI study are presented in Figure 3 below.

**Figure 3: Effect of strong CYP3A4 inhibitor and inducer on the pharmacokinetics of 21-desDFZ**

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A PBPK modeling and simulation analysis was able to reproduce the DDI study results and was further used to evaluate the dose adjustment criteria in children and adolescents with co-administered moderate CYP3A4 inhibitors/inducers (Section 4.6 PBPK Modeling and Simulation). The PBPK simulations predicted approximately similar effect for moderate CYP3A4 inhibitors/inducers when co-administered with deflazacort as the case was with strong CYP3A4 inhibitor/inducer.

**Food Effect Study:** The effect of high-fat meal was evaluated after a single oral dose of the to-be-marketed deflazacort tablet (1 × 36 mg) in study MP-104-CL-026. Administration of deflazacort with a high-fat meal reduced $C_{max}$ by about 30% and delayed $t_{max}$ by about an hour relative to administration under fasting conditions. This indicate lower rate of systemic absorption when deflazacort was administered with high-fat food (Figure 4). Since deflazacort was dosed without any restriction to food intake in the pivotal efficacy study, different dosing regimens (once daily vs once every other day) showed signs of efficacy, and the fact that there is years of clinical experience with deflazacort dosing in DMD, we consider the observed differences in rate of systemic absorption affecting the $C_{max}$ as not clinically significant. As a result, EMFLAZA™ can be given without regard to food. Please refer to 'Section 4.10 Relative BA/BE and Food Effect Study for details of the study design and results.

### *3.3.6 Is there an adequate PK bridge between to-be-marketed formulations and the clinical formulation?*

**Bridging Clinical Trial Formulation to the To-be-Marketed Formulations:**

An indirect PK Bridge was established between the clinical trial formulation and the to-be-marketed formulation. The clinical trials were conducted in the early 1990s and no detailed information on the clinical trial formulation is currently available. Also, there was no PK data collected from these Phase 3 studies. Therefore, direct bridging of the to-be marketed formulation to the clinical trial formulation was not feasible. The following characteristics of deflazacort were considered to address the formulation bridging issue:

1. There are clinical pharmacology studies with different formulations of deflazacort (i.e., oral suspension, tablet and crushed tablet in applesauce) and all these formulations provided exposure within acceptable bioequivalence limits. This suggests that deflazacort absorption is not sensitive to formulation changes.
2. Food effect study showed that a high-fat meal does not affect the extent of exposure (AUC) of deflazacort. This suggests that the *in-vivo* dissolution and subsequently absorption was not changed with changes in the pH and gastrointestinal contents.
3. Based on the physicochemical properties, the estimated fraction of deflazacort absorbed from gastrointestinal tract is relatively high (more than 95 % of the dose). See Section 4.7 for additional details.
4. Clinical efficacy studies used various dosing regimens for deflazacort demonstrating efficacy. For example, Study MP-104-NM-001 tested a 0.9 and 1.2 mg/kg/day of

deflazacort in a once daily regimen. Study MP-104-NM-002 tested a 2 mg/kg dose as every other day regimen. All these dosing regimens showed efficacy in DMD patients, which suggests that variation in peak exposure of deflazacort is unlikely to affect efficacy. In addition, it is also noted that EMFLAZA™ tablet is bioequivalent to Calcort® tablet, which is not approved in the US but is approved in the rest of the world for non-DMD indications.

These observations suggest that the intrinsic properties of deflazacort are sufficient to ensure absorption, regardless of the pH and formulation changes. This also suggests that the to-be-marketed deflazacort formulation is unlikely to have lower bioavailability than the clinical formulation used in the efficacy studies conducted in the early 1990s.

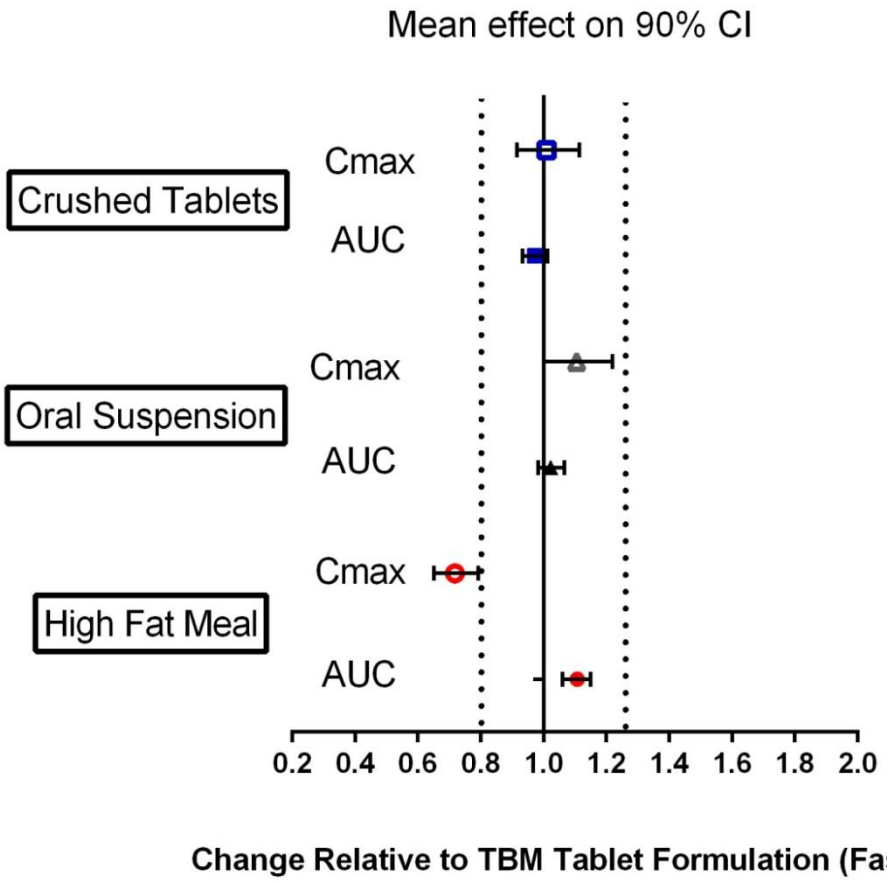
**Bioequivalence of the Oral Suspension Formulation to the Tablet Formulation:**

The relative BA/BE study MP-104-CL-026 assessed the comparative bioavailability of the commercial oral suspension of deflazacort (36 mg/1.58 mL) in apple juice versus intact to-be-marketed tablet formulation (1 × 36 mg).

This study evaluated the pharmacokinetics and safety of deflazacort when administered as a single 36-mg dose under various conditions (fasted, fed, crushed tablet in apple sauce, intact tablet, and oral suspension). The oral suspension and the commercial tablet formulations were bioequivalent and this study provides support for approving the suspension formulation.

The study also showed that the crushed tablets mixed with apple sauce were bioequivalent to intact tablets (Figure 4). Also refer to 'Section 4.10 Relative BA/BE and Food Effect Study for additional details.

**Figure 4 Effect of formulation and food on 21-desDFZ exposure**

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# 4. APPENDICES

## 4.1 Bioanalytical Method Report

The plasma concentrations of 21-desDFZ were determined by a validated LC-MS/MS method using $d^3$-21-desacetyl deflazacort as the internal standard. An aliquot of acidified human plasma (EDTA) containing the analyte and internal standard was extracted using a protein precipitation procedure. The extracted samples were analyzed by an HPLC equipped with an AB SCIEX API 5000™ triple quadrupole mass spectrometer using an electro spray ionization (ESI) source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. The details of the bio-analytical methods used in this NDA are presented in Table 1 below. The methods satisfied the criteria for method validation and application to routine analysis set by the Guidance for Industry: Bioanalytical Method Validation, and hence are acceptable.

**Table 1: Assay validation results for 21-desDFZ in human plasma**

| Analyte/Parameter | 21-desDFZ |
|---|---|
| **Range (ng/ml)** | 1-200 ng/ml |
| **Inter Batch Precision (% CV)** | 2.9 to 5.9% |
| **Inter Batch Accuracy (% Bias)** | -2.7 to 7.7% |
| **Internal standard (IS)** | $d^3$-21-DesDFZ |
| **Reference standard** | 21-DesDFZ |
| **Selectivity** | No significant interference for 21-desDFZ or $d^3$-21-desDFZ (IS) in any of the 10 acidified human plasma (EDTA) lots screened |
| **Recovery (%)** | 93-100% |
| **Stability (% Mean Ratio):** | |
| **Freeze/Thaw Stability** | 6 Cycles (83-86%) |
| **At room temperature** | 307 days (93-96%) |
| **Stock solution -20°C (% Mean , % CV)** | 91 days (98.6, 2.6%) |

### 4.2 Clinical PK/PD Assessments

N.A

### 4.3 Exposure-Response

N.A

### 4.4 Co-Development of Drug and Companion Diagnostic

N.A

### 4.5 Influence of Genetic Markers on PK, Efficacy, or Safety

N.A

## 4.6 PBPK Modeling and Simulation Report

### Background

Deflazacort is a pharmacologically inactive pro-drug which is metabolized completely and rapidly by plasma esterases to the active moiety 21-desDFZ. The proposed dosing regimen for deflazacort is 0.9 mg/kg/day. Plasma concentrations of deflazacort following oral administration are below the limits of quantification while 21-desDFZ is readily detectable. This active metabolite is eliminated rapidly with a plasma half-life of approximately 2-3 hours. The other metabolite identified in humans is the pharmacologically inactive 6-β-hydroxy-21-deascetyl-DFZ. The applicant conducted drug interaction studies to evaluate the effect of strong CYP3A4 inhibitors (clarithromycin) and inducers (rifampin) on the PK of 21-desDFZ in healthy adult subjects taking a single oral dose of deflazacort. Co-administration with clarithromycin increased 21-desDFZ maximal plasma concentration ($C_{max}$) and area under the concentration-time curve (AUC) by 2 and 3 folds respectively. Co-administration of deflazacort with rifampin decreased 21-desDFZ $C_{max}$ and AUC by 92 % and 94 %, respectively. The Applicant also conducted a study in subjects with moderate hepatic impairment and a study in subjects with end stage renal disease (dosed not on dialysis day). These studies showed no clinically significant effect of organ impairment on the exposure of 21-desDFZ [2].

The applicant developed a PBPK model of 21-desDFZ using drug-drug interaction (DDI) data along with the PK profiles of 21-desDFZ in healthy volunteers [1]. The PBPK model was used to predict the exposure of 21-desDFZ in children (4 to 11 years), and adolescents (12 to 16 years) following co-administration of deflazacort and strong or moderate CYP3A4 inhibitors/inducers. The PBPK predictions for the interaction with strong and moderate CYP3A4 inhibitors and inducers in children and adolescents were utilized as supportive information for the proposed dosing recommendations.

The applicant's proposed US prescription information (USPI), states the following:

(b) (4)

This review evaluates the adequacy of the Applicant's PBPK model analyses to support the dosing recommendations in children and adolescents with or without concomitant administration of CYP3A4 modulators.

### Method

All simulations were run using population based PBPK software Simcyp® (V15, a Certara company, Sheffield, UK) [4] and unless stated otherwise, input parameters for 21- desDFZ were derived from the *in-vitro* data and extrapolated to the *in-vivo* parameters as specified in Table 8. The applicant used a minimal PBPK model which considers both liver and intestinal metabolism. The model included a single adjusted compartment that lumps all

the tissues excluding the intestine, liver and portal vein into one compartment. The model assumed a rapid conversion of deflazacort to 21-desDFZ.

The model assumed a linear pharmacokinetics of 21-desDFZ and this assumption was supported by the observed dose proportionality of deflazacort following single-dose oral administration at doses of 3, 6 and 36 mg in 24 healthy adult volunteers [5]. A blood to plasma ratio (B:P) of 2.4 was measured for 21-desDFZ using measurements of total radioactivity in whole blood relative to plasma after a single oral dose of 50 mg [$^{14}$C] deflazacort solution in 3 male healthy subjects [6].

Plasma protein binding (PPB) of 21-desDFZ was reported to have an average value of 39.8 % (Alessandro *et al*., 1980) [6]; Thus, a mean free fraction (fu) value of 0.6 was used. An *in vivo* volume of distribution at steady state (Vss) value for 21-desDFZ following intravenous (IV) administration was not available. Predicted Vss values of 0.35 and 1.31 L/kg were obtained using the methods of Poulin and Thiel [7] and Rodgers and Rowland [8], respectively. Using parameter sensitivity analysis, the Vss was optimized to 0.9 L/kg to give the best fit of the maximal plasma concentration ($C_{max}$) of 21-desDFZ following single oral dose of deflazacort [5].

The model assumed first-order oral absorption kinetics. Values of fraction absorbed (fa) and first order absorption rate constant (ka) for 21-desDFZ were predicted to be 0.96 and 1.18 $h^{-1}$ using apparent permeability (passive only) of 22.7 x $10^{-6}$ cm/s for deflazacort in MDCK cell lines. These values were used as input parameter assuming that at the dose levels studied, P-glycoprotein transporter has been saturated and deflazacort is converted to 21-desDFZ instantaneously. The flow term ($Q_{gut}$) represents a nominal blood flow and is a hybrid parameter reflecting drug absorption rate from the gut lumen, removal of drug from the enterocyte by the enterocytic blood supply and the volume of enterocytes [4]. The $Q_{gut}$ of 21-desDFZ was predicted to be 5.01 L/h using MDCK permeability of 6.3 x $10^{-6}$ cm/s. This parameter was required to calculate the fraction escaping gut metabolism ($F_g$) of 21-desDFZ.

Metabolic intrinsic clearance of 32.4 µl/min/mg protein was derived from *in vitro* data generated from incubations of human liver microsomes with 21-desDFZ. Scaling of this value to a hepatic clearance using well-stirred liver model and combining with the renal clearance of 9 L/h prior to predicting an oral clearance led to value of 86.49 L/h. This is consistent with the observed range for oral clearance (76.6 to 97.1 L/h).

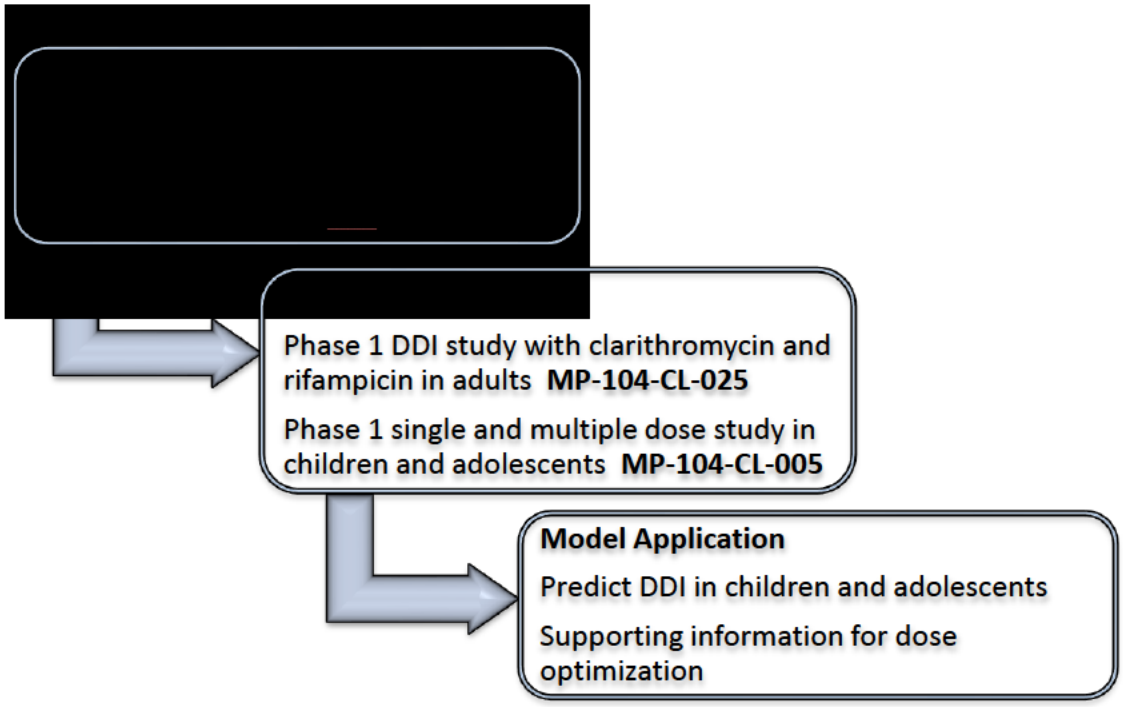
The verification of the PBPK model for 21-desDFZ was based on the observed DDI with clarithromycin and rifampicin (Clinical Study Report: MP-104-CL-025) [2]. Additional verification of the PBPK model in male children (4 to 11 years) and adolescents (12 to 16 years) was conducted using the aforementioned drug model developed in adults using virtual pediatric population in the Simcyp® Simulator [9], followed by comparison with observed data (Clinical Study Report: MP-104-CL-005) (See Figure 5).

The verified model was used for the prediction of the change in exposure of 21-desDFZ in children (4 to 11 years) and adolescents (12 to 16 years) with DMD following co-administration with strong or moderate CYP3A4 inhibitors/inducers at steady state.

For model development and verification, PK simulations using virtual subjects, matched as closely as possible with respect to age and sex to those in the corresponding actual studies,

and according to the same study design were employed. Unless otherwise stated, ten (10) trials with 16 subjects were run for each study. For model applications (simulation of scenarios not tested), simulations were run using 16 and 8 virtual subjects for the children and adolescents categories respectively with10 trials for each age group with/without co-administration of a CYP3A4 modulator. The input parameters of the compound library files for clarithromycin, fluconazole, rifampicin and efavirenz were the default settings in Simcyp® V15 software unless otherwise stated.

**Figure 5 Development and application of a PBPK model for Deflazacort**

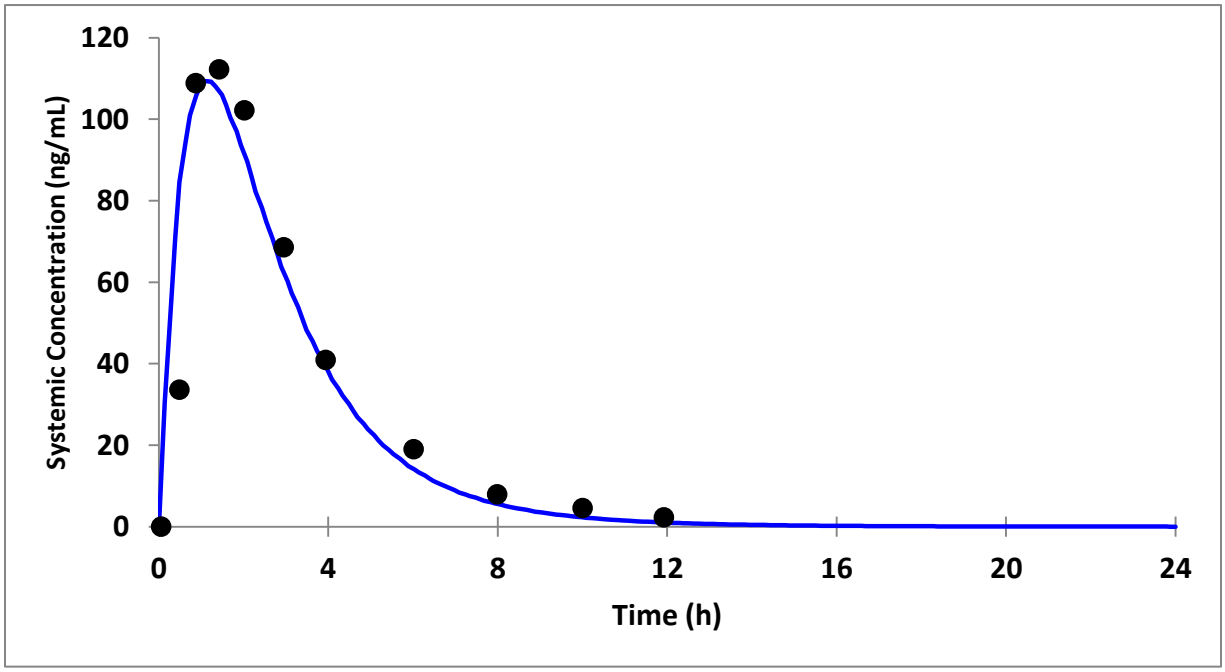



## Key Review Questions

### *Can the PBPK model predict PK of 21-desDFZ?*

Yes, the model was able to predict the 21-desDFZ concentration-time profiles in plasma after single oral dose administration of 36 mg in healthy volunteers. Ten virtual trials of 24 healthy male subjects aged 20 to 40 years receiving an oral dose of 36 mg deflazacort were simulated. The simulated and observed (Rao *et al.*, 1996 [5]) plasma concentration-time profiles were compared in Figure 6 showing that the model predictions are close to the observed values.

**Figure 6 Observed (black circles) and PBPK-predicted (blue line) average plasma concentration-time profile of 21-desDFZ after a 36 mg single oral dose of deflazacort.**

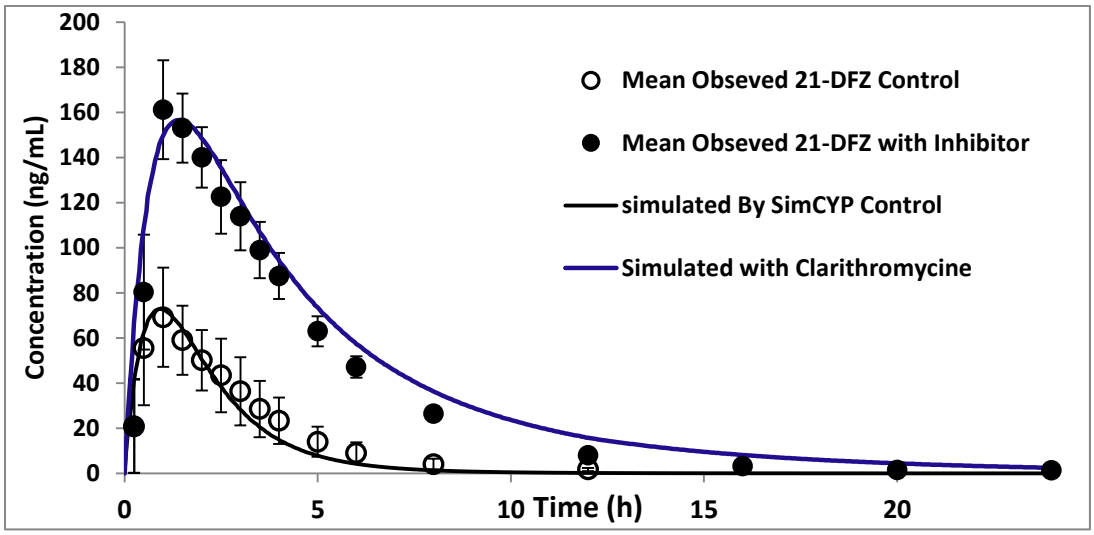



*Source: FDA reviewer re-simulated under condition described by applicant (Figure 4, PBPK report [1]) using final PBPK model*

***Can the PBPK model predict the effect of CYP3A4 modulators on the PK of 21-desDFZ?***

Yes. The PBPK model was able to describe the observed DDI with clarithromycin, a strong CYP3A4 inhibitor (Clinical Study Report: MP-104-CL-025). Ten virtual trials of 29 healthy subjects (28% female) aged 23 to 55 years receiving a single oral dose of deflazacort (18 mg) on the last day of 4 days of dosing of clarithromycin (500 mg twice daily, BID) were simulated. The increase in exposure of 21-desDFZ was compared with the observed data from the DDI study. Simulated PK profiles and geometric mean $C_{max}$ and AUC and corresponding ratios are shown in Figure 7 & Figure 6 and Table 2. All parameters were within 1.25-fold of the corresponding observed data.

**Figure 7 Simulated and observed mean plasma concentration-time profiles of 21-desDFZ after a single oral dose of 18 mg deflazacort on the last day of 4 days of dosing of clarithromycin (500 mg BID), a strong CYP3A4 inhibitor.**




*Source: FDA reviewer re-simulated under condition described by applicant (Figure 6 and 7, PBPK report [1]) using submitted PBPK models.*

**Table 2 Simulated and observed $C_{max}$ and $AUC_{(0,\infty)}$ values (geometric mean) and corresponding ratios for 21-desDFZ after a single oral dose of 18 mg deflazacort on the last day of 4 days of dosing of clarithromycin (500 mg BID).**

| | Deflazacort Alone | | Plus clarithromycin | | Ratio | |
|---|---|---|---|---|---|---|
| | $C_{max}$ (ng/mL) | $AUC_{(0,\infty)}$ (ng/mL*h) | $C_{max}$ (ng/mL) | $AUC_{(0,\infty)}$ (ng/mL*h) | $C_{max}$ | $AUC_{(0,\infty)}$ |
| Simulated | 96.4 | 183 | 151 | 870 | 2.1 | 4.2 |
| Trial Range | (60.2-80.3) | (161-216) | (134-173) | (627-960) | (2-2.4) | (3.6-5.2) |
| Observed | 75.5 | 218 | 170 | 737 | 2.25 | 3.37 |

Source: Table 3 [1]

The model was not able to capture the exposure of 21-desDFZ when the drug was co-administered with rifampin (a strong CYP3A4 inducer). The observed reduction in $C_{max}$ and AUC of 21-desDFZ in the presence of rifampicin was under-predicted by 3.5-fold and 2.0-fold, respectively Table 3).**Table 3** Significant under-prediction of the effect of rifampicin using PBPK has been reported before. The applicant suggested that the under prediction may be because the induction of P-gp was not considered in the simulation of DDI between deflazacort and rifampicin. Intestinal efflux by P-gp and induction of P-gp were not incorporated in the models of 21-desDFZ and rifampicin, respectively. Under

baseline conditions, P-gp mediated efflux of deflazacort is saturated. However, rifampicin is an inducer of P-gp as well. When co-administered with rifampicin, P-gp mediated intestinal efflux may play an important role by limiting oral absorption of deflazacort.

**Table 3: Geometric mean simulated and observed $C_{max}$ and $AUC_{(0,\infty)}$ values and corresponding ratios of 21-desDFZ after a single oral dose of 18 mg deflazacort on the last day of 10 days of dosing of rifampicin (600 mg once daily, QD).**

| | Deflazacort alone | | Plus Rifampicin | | Ratio | |
|---|---|---|---|---|---|---|
| | $C_{max}$ (ng/mL) | $AUC_{(0,\infty)}$ (ng/mL*h) | $C_{max}$ (ng/mL) | $AUC_{(0,\infty)}$ (ng/mL*h) | $C_{max}$ | $AUC_{(0,\infty)}$ |
| Simulated | 69 | 180 | 15.4 | 2 | 0.22 | 0.15 |
| Trial Range | (61.5-83.7) | (157-216) | (11.9-20.6) | (20.0-36.4) | (0.18-0.30) | (0.12-0.21) |
| Observed | 79 | 226 | 6.1 | 14.3 | 0.06 | 0.08 |

Source: Table 4 [1]

***Can the PBPK model predict the PK in children and adolescents?***

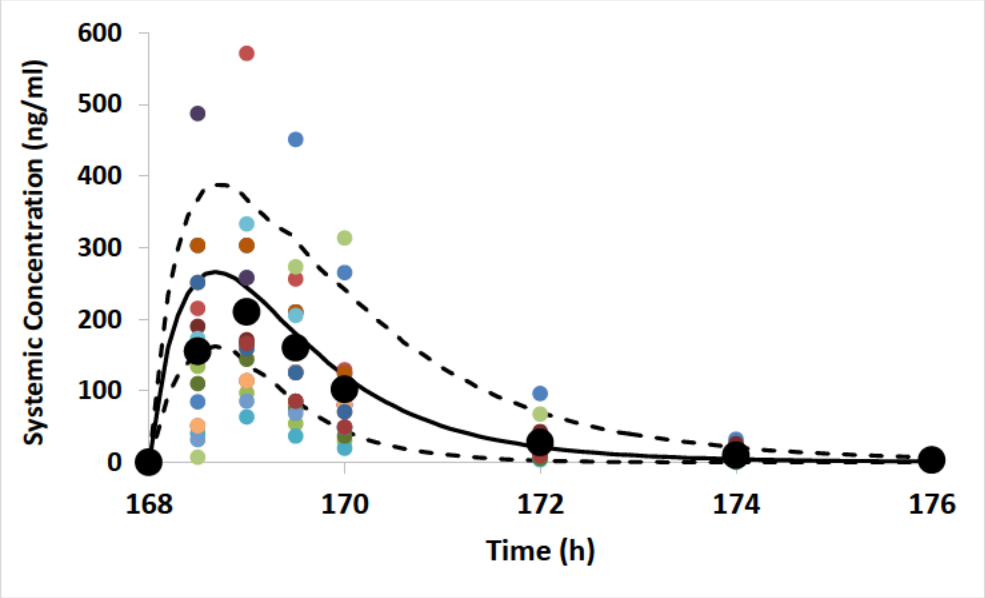
Yes. Using the PBPK model developed using adult data, the applicant simulated plasma concentrations of 21-desDFZ in male children (4-11 years) and adolescents (12-16 years) and compared the simulations with observed data. Mean simulated and observed (Clinical Study Report: MP-104-CL-005) plasma concentrations of 21-desDFZ on the last day of 8 days of daily dosing of deflazacort (0.8 mg/kg daily) in children aged 4 to 11 years with DMD are shown in Figure 8. Overall, the PBPK model reasonably described observed PK of 21-desDFZ in children. According to the applicant, the median and mean dose of deflazacort in study MP-104-CL-005 was actually 0.8 mg/kg based on available tablet strengths and patient weight bands, although the protocol indicated that the recommended dose was 0.9 mg/kg. Simulation results comparing 0.9 mg/kg and 0.8 mg/kg dose are presented in Table 4. In addition, the model was able to describe 21-desDFZ in adolescents. Mean simulated and observed (Clinical Study Report: MP-104-CL-005) plasma concentrations of 21-desDFZ on the last day of 8 days of daily dosing of deflazacort (0.9 mg/kg daily) in male adolescents aged 12 to 16 years with DMD are shown in Figure 9. The predicted mean and observed geometric mean $C_{max}$ and AUC values for 21-desDFZ are shown in Table 4. For both children and adolescents, the simulated $C_{max}$ and AUC values are within 1.25-fold of observed data.

**Table 4 Simulated and observed geometric mean $C_{max}$ and $AUC_{(0,8)}$ values for 21-desDFZ on the last day of 8 days of dosing of deflazacort in children (4-11 years) and adolescents (12-16 years).**

| | Children | | | | Adolescents | |
|---|---|---|---|---|---|---|
| | 0.8 mg/kg | | 0.9 mg/kg | | 0.9 mg/kg | |
| | $C_{max}$ (ng/mL) | $AUC_{(0,8)}$ (ng/mL*h) | $C_{max}$ (ng/mL) | $AUC_{(0,8)}$ (ng/mL*h) | $C_{max}$ (ng/mL) | $AUC_{(0,8)}$ (ng/mL*h) |
| Simulated | 261 | 499 | 294 | 562 | 268 | 587 |
| Observed | 214 | 374 | 214 | 374 | 329 | 567 |

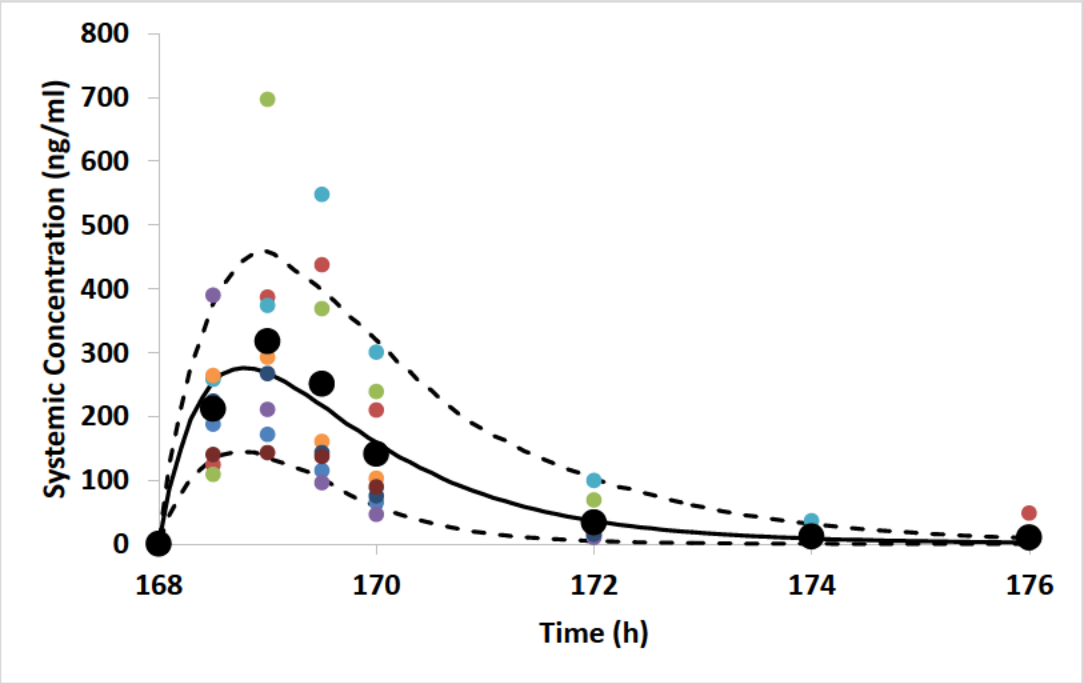
Source: Table 7 and 8 [1]

**Figure 8. Simulated mean (lines) and observed (symbols; n=16; Clinical Study Report: MP-104-CL-005) plasma concentrations of 21-desDFZ on the last day of 8 days of dosing of deflazacort (0.8 mg/kg) in male children (aged 4 to 11 years) with DMD. The solid line is the mean data for the simulated population, and the dashed lines are the 5th and the 95th percentiles. The black circles represent the mean observed data based on all 16 subjects.**




Source: Figure 16 [1].

**Figure 9: Simulated mean (lines) and observed (symbols; n=8; Clinical Study Report: MP-104-CL-005) plasma concentrations of 21-desDFZ on the last day of 8 days of dosing of deflazacort (0.9 mg/kg) in male adolescents (aged 12 to 16 years) with DMD. The solid line is the mean data for the simulated population, and the dashed lines are the 5th and the 95th percentiles. The black circles represent the mean observed data based on all 8 subjects.**




Source: Figure 18 [1]

***Can the PBPK model be used to support dose adjustments for deflazacort when co-administered with CYP3A4 inhibitors and inducers in children and adolescents?***

Yes, the PBPK model of 21-desDFZ has been verified for CYP3A4 contribution (as described in 4.2 above) and effect of age on 21-desDFZ PK down to 4 years old (as described in 4.3 above). The model can be used to simulate the effect of CYP3A4 modulator, especially CYP3A4 inhibitors on the PK of 21-desDFZ in children (4-11 years old) and adolescents. Its also noted that it's not expected to have different results for children older than two years old

The model was used to predict the mean plasma concentrations of 21-desDFZ in male children aged (4 to 11 years old) and in adolescents (12-16 years old) after dosing of deflazacort (0.9 mg/kg) in the absence of and presence of a strong [clarithromycin 7.5 mg/kg QD] or a moderate CYP3A4 inhibitors [fluconazole 6 mg/kg QD]. Results for the predicted change in $C_{max}$ and AUC of 21-desDFZ at steady state are indicated in Table 5.

The magnitude of interaction between 21-desDFZ as the victim and clarithromycin as a CYP3A4 inhibitor was predicted to be similar in children, adolescents and adults (Table 5 versus Table 2).

**Table 5 Predicted geometric mean $C_{max}$ and AUC ratios of 21-desDFZ following co-administration of CYP3A4 inhibitors with deflazacort (0.9 mg/kg).**

| | Children | | Adolescents | |
|---|---|---|---|---|
| | $C_{max}$ Ratio | AUC Ratio | $C_{max}$ Ratio | AUC Ratio |
| Clarithromycin (7.5 mg/kg) | 1.97 | 3.85 | 2.14 | 4.31 |
| Fluconazole (6 mg/kg) | 1.96 | 3.61 | 2.10 | 3.97 |

Source: Table 9 [1]

The model was not able to capture the exposure of 21-desDFZ with CYP3A4 inducer (rifampicin). The reduction in $C_{max}$ and AUC of 21-desDFZ in the presence of rifampicin was under-predicted by 3.5-fold and 2.0-fold, respectively Table 3. However, the model was used to predict the mean plasma concentrations and of 21-desDFZ in pediatric subjects of the same age groups after dosing of deflazacort (0.9 mg/kg) in the absence of and presence of strong [ rifampicin 10 mg/kg QD] and moderate [efavirenz 350 mg QD] CYP3A4 inducers. Results for the predicted change in $C_{max}$ and AUC of 21-desDFZ at steady state are indicated in Table 6.

**Table 6 Predicted geometric mean $C_{max}$ and AUC ratios of 21-desDFZ following coadministration of CYP3A4inducers with deflazacort (0.9 mg/kg)**

| | Children | | Adolescents | |
|---|---|---|---|---|
| | $C_{max}$ Ratio | AUC Ratio | $C_{max}$ Ratio | AUC Ratio |
| Rifampicin (10 mg/kg) | 0.31 | 0.22 | 0.24 | 0.17 |
| Efavirenz (350/600 mg QD) | 0.43 | 0.29 | 0.43 | 0.30 |

Source: Table 9 [1]

It should be noted that the magnitude of interaction between 21-desDFZ as the victim and clarithromycin or rifampicin as the perpetrators was predicted to be similar in children, adolescents and adults (AUC ratios were 4.18 and 0.15, respectively).

The recommended dose adjustments based on $C_{max}$ and AUC matching are shown in Table **7**. Based on AUC, a 3-fold reduction is needed when deflazacort is co-administered with a

strong CYP3A4 inhibitor, which supports the proposed dosing recommendations: (b) (4)

The simulation results also suggested that increasing the dose of deflazacort up to 3 and 5.4 times after co-administration of moderate (efavirenz) and strong (rifampicin) CYP3A4 inducers is needed to match 21-DFZ exposure in the absence of an inducer. It was eventually concluded that the co-administration of deflazacort with CYP3A4 inducers should be avoided.

**Table 7 Dose adjustments recommended for DFZ in the presence of CYP3A4 modulators by the applicant.**

| | Recommended dose of DFZ in the presence of a | |
|---|---|---|
| | Based on $C_{max}$ | Based on AUC |
| Clarithromycin | 0.4 to 0.5 | 0.2 to 0.3 |
| Fluconazole | 0.4 to 0.5 | 0.2 to 0.3 |
| Rifampicin | 3.6 | >5.4 |
| Efavirenz | 2.0 | 3.0 |

Source: Table 10 [1]

***Summary of PBPK model limitations and simulations of the effect of organ impairment on the PK of 21-desDFZ***

As mentioned above (Section 4.2), intestinal efflux by P-gp and induction of P-gp were not considered in the models of 21-desDFZ and rifampicin, respectively. These limitations are likely the causes of under prediction of the effect of rifampicin on the PK of 21-desDFZ.

The sponsor also simulated exposure of 21-dseDFZ in subjects with moderate hepatic impairment and subjects with end stage renal disease (ESRD). These simulations were conducted using PBPK model developed in healthy subjects in virtual organ impairment populations implemented the PBPK platform [10, 11]. Model simulated and observed geometric mean $C_{max}$ and AUC values of 21-desDFZ are compared in Table 9. Because confidence is low to apply PBPK to prospectively predict drug PK in subjects with hepatic or renal impairment [12], these simulations are considered exploratory.

## Conclusions

The PBPK model of 21-desDFZ, verified for CYP3A4 contribution and effect of age (4-16 years) on 21-desDFZ PK, is adequate to simulate the effect of CYP3A4 modulators on the PK

of 21-desDFZ in children (4-11 years old) and adolescents (12-16 years old) taking deflazacort.

Based on the simulated $C_{max}$ and AUC in children and adolescents with and without a CYP3A4 modulator, (i) deflazacort dose should be reduced by 3-fold when a moderate or strong CYP3A4 inhibitor is co-administered; and (ii) co-administration of moderate and strong CYP3A4 inducers should be avoided.

## Abbreviations (usually from applicant's report)

AUC, area under the concentration-time curve; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; BID., twice daily dosing; B/P, blood to plasma ratio; $C_{max}$, maximal concentration in plasma; $C_{max}R$, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; $CL_{int}$, intrinsic clearance; DDI, drug-drug interaction; EC50, calibrated concentration causing one-half of maximum effect; Emax, maximum fold induction; F, bioavailability; fa, fraction absorbed; Fg, fraction that escapes intestinal metabolism; fu, unbound fraction in plasma; $fu_{inc}$, unbound fraction in incubation medium; $fu_{mic}$, unbound fraction in microsomes; $fu_{gut}$, apparent unbound fraction in enterocytes; $Ind_{max}$, maximal fold induction; ka, first order absorption rate constant; Kp, tissue-to-plasma partition coefficient; Ki, reversible inhibition constant; Km, Michaelis Menten constant; $LogP_{o:w}$, logarithm of the octanol-water partition coefficient; NA, not applicable; PBPK, Physiological-based Pharmacokinetic; $P_{eff}$, predicted effective intestinal permeability; P-gp, P-glycoprotein; QD, once daily dosing; $Q_{gut}$, a hypothetical flow term for the intestine absorption model; Vss, volume of distribution at steady state; $V_{max}$, maximal velocity. ESRD, End stage renal disease; Child Pugh B: moderate hepatic impairment.

The PBPK reviewers acknowledge the scientific discussions with Dr. Yuching Yang and Dr. Zhongqi Dong.

## Appendix Tables

### Table 8. PBPK Model Input Parameters

| Parameter | 21-desDFZ | Source/Reference |
|---|---|---|
| MW | 399.48 | Provided by Marathon |
| clog P | 1.96 | ACD software |
| B:P | 2.4 | Assandri *et al.,* 1980 |
| Compound type | acid | ACD software |
| pKa | 5.52 | ACD software |
| fu | 0.6 | Assandri *et al.,* 1980 |
| $V_{ss}$ (L/kg) | 0.9 | Optimized (initial estimate (1.3 L/kg) was generated using Rodger's method and optimized to 0.9 L/kg to give the best fit usng sensitivity analysis) |
| fa | 0.96 | Predicted from MDCK data (Sun *et al.*,2002) |
| ka ($h^{-1}$) | 1.19 | |
| MDCK data (x $10^{-6}$ cm/s) | 22.7 | Marathon Study Number: MP-104-NC-055 |
| Qgut (L/h) | 5.01 | Predicted from MDCK data (Sun *et al.*,2002) |
| CYP3A4:<br><br>$CL_{int,u}$ (µl/min/mg protein) | 32.4 | MP-104-NC-011 |
| $CL_R$ (L/h) | 9.00 | Assandri *et al.,* 1980 |

Source: Table 2 [1]

**Table 9 Simulated and observed geometric mean $C_{max}$ and AUC values for 21-desDFZ after a single oral dose of deflazacort (36 mg) in adults.**

| | Simulated $C_{max}$ | Observed $C_{max}$ | Simulated AUC (0-inf) | Observed AUC (0-inf) |
|---|---|---|---|---|
| | | **Renal impairment** | | |
| **Healthy** | 137 | 139 | 394 | 447 |
| **ESRD** | 95.4 | 120 | 352 | 404 |
| **Ratio (ESRD/Healthy)** | 0.70 | 0.86 | 0.89 | 0.90 |
| | | **Hepatic impairment** | | |
| **Healthy** | 149 | 172 | 428 | 529 |
| **Child Pugh B** | 256 | 204 | 1342 | 513 |
| **Ratio (Child Pugh B/Healthy)** | 1.72 | 1.19 | 3.14 | 0.97 |

Source: Table 5 and Table 6 [1]

## References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9. Johnson, T.N., Rostami-Hodjegan, A. & Tucker, G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet 45, 931-56 (2006).
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11. Johnson TN, Boussery K, Rowland Yeo K, Tucker GT and Rostami_Hodjegan A. A semi-mechanistic model to predict the effects of of liver cirrhosis on drug clearance. Clin Pharmacokinet 2010; 49: 189- 206
12. Wagner C, Zhao P, Pan Y, Hsu V, Grillo J, Huang SM, Sinha V. Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK. CPT-Pharmacometrics Syst Pharmacol. 2015 4(4):226-30.

## 4.7 Prediction of Fraction Absorbed After Oral Administration

The purpose of this review is to predict the fraction absorbed (Fa, the fraction disappearing from the lumen) of deflazacort based on the physicochemical properties using the advanced compartmental absorption and transient model (ACAT) in GastroPlus® version 9. This exercise is conducted to further support the PK bridge for the clinical trial formulation to the to-be-marketed tablet formulation. The ACAT model in GastroPlus® 9 was used to calculate the fraction absorbed (Fa) of deflazacort after oral administration of 36 mg tablet based on the extrapolated permeability values from *in-vitro* permeability data, along with the solubility data, and the particle size distribution for deflazacort. Input parameters used for this prediction is summarized in Table 10. Predicted Fa was more than 95%. The absorption number, (Small intestine transient time/small intestine absorption time) and the dissolution number, (small intestine transit time by the longest dissolution time at pH 1, 4.5 or 6.8) were relatively high (6.9 and 2.4 for the absorption and dissolution number respectively). These findings suggest that the intrinsic properties of the drug substance is sufficient to ensure complete absorption and changes in formulation excipients will not contribute significantly to drug absorption.

It is also noted that the estimate of fraction absorbed for deflazacort used in the Simcyp® based PBPK model for predicting drug interaction was also estimated to be almost complete (higher than 95%). Under this assumption of high Fa value, the model generated DDI results and other clinical PK date were successfully reproduced. The fraction absorbed in Simcyp® model was estimated from the in-vitro permeability data and suggested a complete absorption of deflazacort (section 4.6). This Finding support the argument that EMFLAZA™ tablet is unlikely to have a Fa value lower than the clinical trial formulation and under expsure is unlikely to be a concern.

On the other hand, Calcort® a drug product of deflazacort approved outside the US for other non-DMD indications was found to be bioequivalent to EMFLAZA™. This will add additional support that EMFLAZA™ will not result in higher plasma concentration that was not tested in humans before.

**Table 10: Input Parameters for the prediction of Deflazacort Fraction Absorbed Using GastroPlus®**

| Parameter | Deflazacort | Source/Reference |
|---|---|---|
| MW | 441.53 | Provided by Marathon |
| log P | 2.4 | ADMET Predictor |
| Compound type | acid | ACD software |
| pKa | 5.52 | ACD software |
| Solubility (mg/ml) | pH 2: 0.18, pH4.5:0.1, pH:6.8:0.1 | CMC Report |
| Particle Size (uM) | (b) (4) | CMC Report |
| Permeability | 22.7x10-6 | From in-vitro Permeability |
| Diffusion Coefficient | 0.61 cm^2/sec x10-5 | ADMET Predictor |
| Mean Precipitation time (MPT) | (9-900) sec | GastroPlus (100 fold decrease in MPT was tested) |
| Dose Volume | 250 mL | |
| Dosage Form | 36 mg Oral Tablet | |
| Physiology | Human Physiology Fasted | GastoPlus 9.0 |
| Absorption Scaling Factor (ASF) | Opt logD Model SA/V 6.1 | GastoPlus 9.0 |
| Dissolution Model | (b) (4) Dissolution Model | (b) (4) |

Source: Study report MP-104-NC-062; Drug substance general properties, \\cdsesub1\evsprod\nda208684\0000\m3\32-body-data\32s-drug-sub\deflazacort-sterling\32s1-gen-info\32s13-general-properties.pdf

## 4.8 Population PK Analysis

**Background**

Sponsor quantified the effect of (A) Age (B) Sex (C) Race/Ethnicity on the pharmacokinetics of 21-desDFZ (active metabolite of deflazacort) using population PK analysis methodology. In the submitted population PK analysis report (MP-104-NC-063), the objectives of conducting these analyses were stated as:

- Combine PK data of 21-desDFZ after oral administration of deflazacort (DFZ) collected in a total of five clinical studies including subjects enrolled in drug-drug interaction (DDI), renal, hepatic, DMD pediatric and relative bioavailability trials.
- Perform a population PK analysis and explore the effect of body weight, formulation, dose, disease status and other covariates of interest on PK parameters of 21-desDFZ.

In addition, the sponsor also submitted plans for simplifying the dosing regimen and including different dose levels based on ambulatory status of the patient.

**Data**

A brief description of the studies included in the analysis is provided below.

- Study MP-104-CL-005 was a Phase 1 multi-center study to evaluate the PK of 21-desDFZ and the safety of DFZ after oral administration of DFZ tablets to children and adolescent subjects with DMD.
- Study MP-104-CL-023 was a Phase 1 study to determine the effect of hepatic impairment on the PK of the active DFZ metabolite, 21-desDFZ in subjects with moderate hepatic impairment.
- Study MP-104-CL-024 was a Phase 1 study to determine the effect of renal impairment on the PK of the active DFZ metabolite, 21-desDFZ in subjects with end-stage-renal disease (ESRD).
- Study MP-104-CL-025 was a Phase 1 study, two-arm, to evaluate the potential effects of multiple doses of rifampicin (CYP3A4 inducer) and clarithromycin (CYP3A4 inhibitor) on the single dose PK of DFZ in healthy subjects.
- Study MP-104-CL-026 was a Phase 1, single-dose, five period crossover study to compare food effect and bioavailability of DFZ formulations in healthy volunteers.

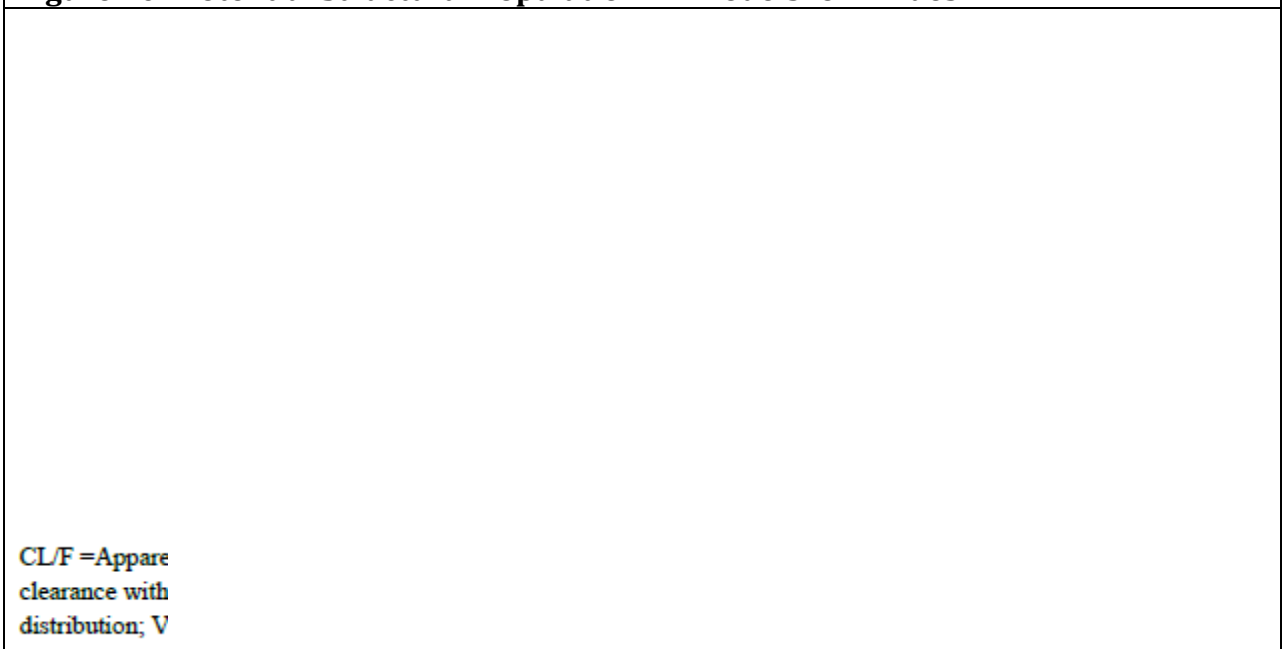
More information on the number of subjects, dosage and PK sampling time can be obtained from **Table 11** below.

| **Table 11. Summary Description of Studies Included in the Population PK Analysis** |
| --- |
| |
| Source : Table 1 on Page 12 of mp-104-nc-063.pdf |

**Sponsor's Analysis**

The population PK modeling and simulations were performed using Phoenix® NLME™ (Version 1.3). Various compartmental PK models were tested to assess the PK of 21-desDFZ, which include one-, two- or three-compartment disposition with linear absorption/ biotransformation (first order) and linear elimination, as presented in **Figure 10**.

**Figure 10. Potential Structural Population PK Models for 21-desDFZ**




Source : Figure 1 on Page 16 of mp-104-nc-063.pdf

Model evaluation and selection of the base structural model was based on:

- Model acceptability based on the pharmacological and physicochemical properties of the drug
- Standard statistical criteria of goodness-of-fit such as the log-likelihood difference between rival models (e.g. a decrease in the minimum objective function (MOF) value, accuracy of parameter estimation).

The following diagnostic plots were performed to evaluate the population PK models:

- Observed concentrations versus population predicted concentrations and individual predicted concentrations with a line of identity and a trend line (linear and log scales).
- Observed concentrations versus time with trend lines of observed concentrations and population predicted concentrations.
- Conditional weighted residuals versus population predicted concentrations with zero line and a trend line.
- Conditional weighted residuals versus time after the 1st dose and time after last dose with zero line and a trend line.
- Quantiles-quantiles plot of conditional weighted residuals (QQ plot).

***Covariate Analysis***

The intrinsic and extrinsic factors explored in the covariate analysis are presented below:

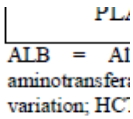
*Intrinsic Factors Potentially Relevant to PK of 21-desDFZ*
- Body weight: Continuous
- Age: Continuous
- Sex
- Race
- Markers of renal function: baseline CrCL
- Markers of liver function: BILI, AST, ALT, and ALP
- Health Status (i.e., healthy, ESRD, hepatic impairment, DMD)
- Platelets

*Extrinsic Factor Potentially Relevant to PK of 21-desDFZ*
- Drug-Drug interaction (DDI) with rifampicin and with clarithromycin
- Fed status (fasted vs high-fat fed)
- Formulation of administered dose of DFZ (Marathon commercial tablet 36 mg, research tablet 6 mg, Marathon crushed tablet, Marathon oral suspension)

**Table 12** and **Table 13** provide descriptive statistics of continuous and categorical covariates included in the analysis.

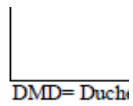
Of the 159 subjects included in the population PK dataset, a higher proportion of males was included in the analysis (i.e., ratio of male and female subjects was 3.82:1), since DMD disease only affects boys. 72.3% and 20.1% of the subjects were White and Black or African American, respectively. Subjects were aged from 4 to 64 years old with a mean value of 39.1 years old. Baseline body weight ranged from 18.2 to 126 kg and DMD pediatric patients weighted from 18.2 to 95.9 kg with a median of 39.1 kg. The percentages of patients with renal and hepatic impairment were 5.0% each (8 patients with ESRD and 8 with hepatic impairment), while 15.1 % of the subjects were identified with DMD (n= 24). Most of the subjects (n=114) were administrated 6 mg commercial tablets of DFZ while only 45 were given the 36 mg Marathon tablets, 36 mg crushed Marathon tablets and/or syrup of DFZ. These subjects (28.3%) were exposed to fasted and high-fat meal to assess the impact of food on DFZ absorption/biotransformation. Of all the 159 subjects, only 29 were exposed before the single DFZ administration to 10 days concomitant medication of 600 mg once daily (QD) of rifampicin while 28 subjects were exposed before the single DFZ administration to four days of 500 mg twice daily (BID) clarithromycin.

**Table 12. Descriptive Statistics of Continuous Covariates at Baseline**




Source : Table 3 on Page 21 of mp-104-nc-063.pdf

**Table 13. Descriptive Statistics of Categorical Covariates at Baseline**

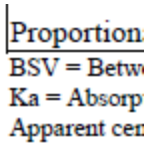



Source : Table 5 on Page 22 of mp-104-nc-063.pdf

**Model Build-Up and Discrimination**

One-, two- and three-compartment population PK models with linear absorption were evaluated by fitting to the concentration-time data of 21-desDFZ collected in a total of 159 subjects. Various residual error (additional, proportional and mixed) and BSV models were evaluated. A two-compartment model with linear absorption/biotransformation and linear elimination was retained based on the MOF value and goodness-of-fit. Independent (i.e., diagonal) BSVs were included on absorption rate (Ka), CL/F, V/F, apparent inter-compartmental clearance (CL2/F) and apparent peripheral volume of distribution (V2/F). The mixed residual error model (additive and proportional) resulted in lower MOF values and was thus preferred. Typical values of PK parameters as well for the structural base PK model of 21-desDFZ are presented in **Table 14**.

**Table 14. Typical Values of Base Population PK Model for 21-desDFZ**


Proportion
BSV = Betw
Ka = Absorp
Apparent cer

Source : Table 6 on Page 24 of mp-104-nc-063.pdf

Graphical representations of goodness-of-fit of the base structural population PK model for 21-desDFZ are presented in **Figure 11**.

**Figure 11. Goodness-of-Fit of the Base Population PK Model for 21-desDFZ**


Source : Figure 2 on Page 25 of mp-104-nc-063.pdf

The following covariate effects were included in the full population PK model of 21-desDFZ:

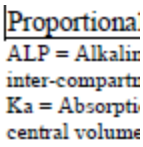
- Frel: fed status (fast vs high fat meal),
- Tlag: fed status (fast vs high fat meal),
- Ka: baseline body weight, fed status, health status (DMD vs others), formulation (Marathon tablet 36 mg, commercial tablet 6 mg, Marathon crushed tablet vs Marathon oral suspension),
- CL/F: baseline body weight, health status (DMD vs others), drug-drug interaction (no co-medication, rifampicin vs clarithromycin),
- V/F: baseline body weight, health status (DMD vs others),
- CL2/F: baseline body weight,
- V2/F: baseline body weight.

The full population PK model was thus reduced by keeping in the model only the covariates with relevant effects

The following covariate effects were included in the final population PK model:
- Frel: fed status (fast vs high fat meal),
- Ka: fed (fast vs high fat meal) and health status (DMD vs others),
- CL/F: health status and drug-drug interaction (no co-medication, rifampicin vs clarithromycin),
- V/F: baseline body weight, health status (DMD vs others), PLAT and ALP,
- V2/F: baseline body weight.

The typical values of the final population PK model are presented in **Table 15**.

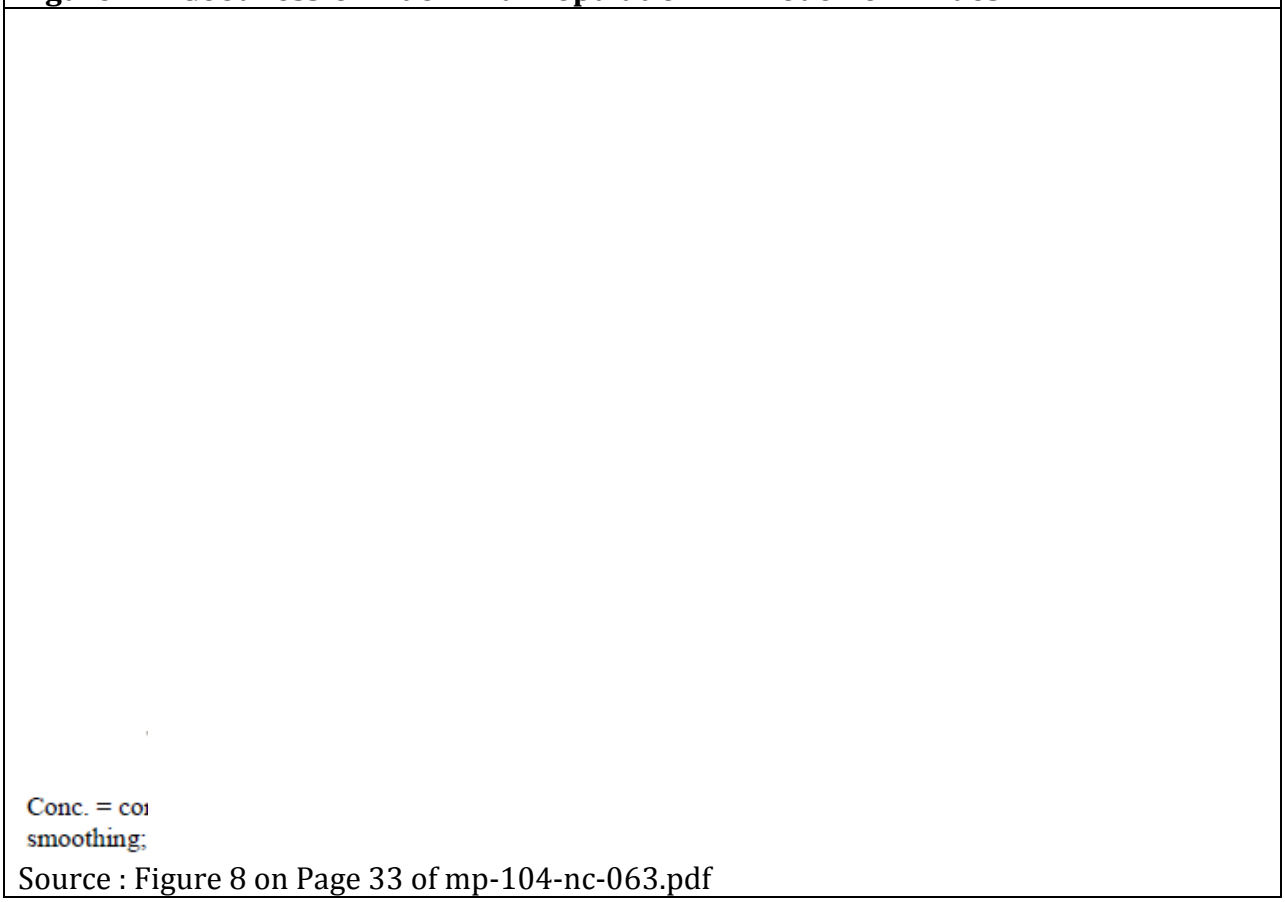
**Table 15. Typical Values of Final Population PK Model for 21-desDFZ**




Source : Table 7 on Page 30 of mp-104-nc-063.pdf

Goodness of fit of the final population PK model for 21-desDFZ is presented in **Figure 12**.

**Figure 12. Goodness-of-Fit of Final Population PK Model for 21-desDFZ**

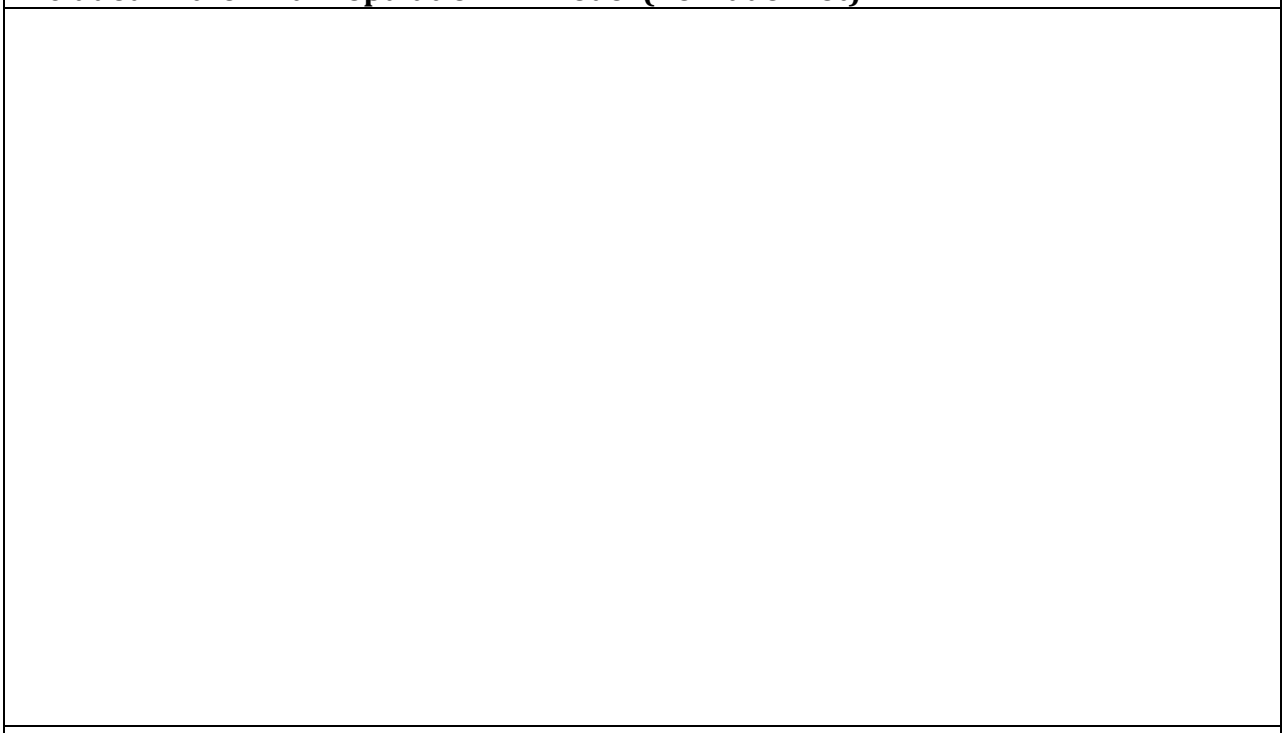


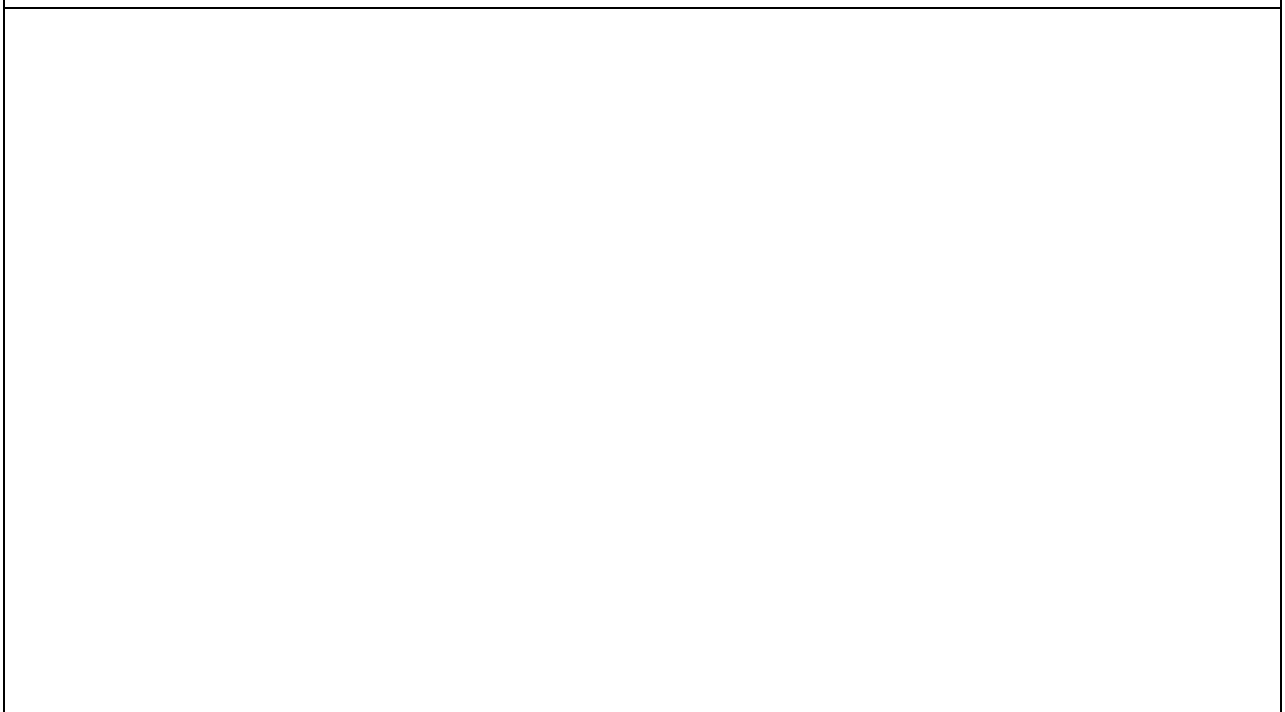

Source : Figure 8 on Page 33 of mp-104-nc-063.pdf

Covariate effects on CL/F and V/F based on the range values of body weight, ALP and PLAT are depicted using tornado plots presented in **Figure 13**.

**Figure 13** provides multiplicative factors of CL/F values corresponding to the categorical covariates included in the population PK model. Effect of rifampicin is likely the most important covariate included in the model by increasing CL/F by a factor 14.04. **Figure 13** provides V/F values corresponding to ranges of body weight observed in adults and pediatric subjects included in the population PK analysis. The range of body weight observed in pediatric DMD patients (i.e., 18.2 to 95.9 kg) is expected to affect the relative V/F of 21-desDFZ (typical value 7.30 L/h) by multiplicative factors of 0.36 and 1.27 while effect of DMD status is expected to increase V/F by a factor of 2.48. Range of adult body weight would affect the typical V/F by multiplicative factor of 0.77 and 1.56.

**Figure 13. Typical Covariates Effects on CL/F (Top), V/F (Bottom) of 21-desDFZ included in the Final Population PK Model (Tornado Plot)**





Source : (Top) Figure 6 on Page 31 (Bottom) Figure 7 on Page 32 of mp-104-nc-063.pdf

**Labeling statements in Section 12.3 of the proposed label based on population pharmacokinetic analyses**


**Reviewer's Analysis**

**Aim**

To verify labeling statements proposed by the sponsor. This involved executing the base and final population pharmacokinetic model. Diagnostic plots were also generated to understand adequacy of the pharmacokinetic model developed by the sponsor.

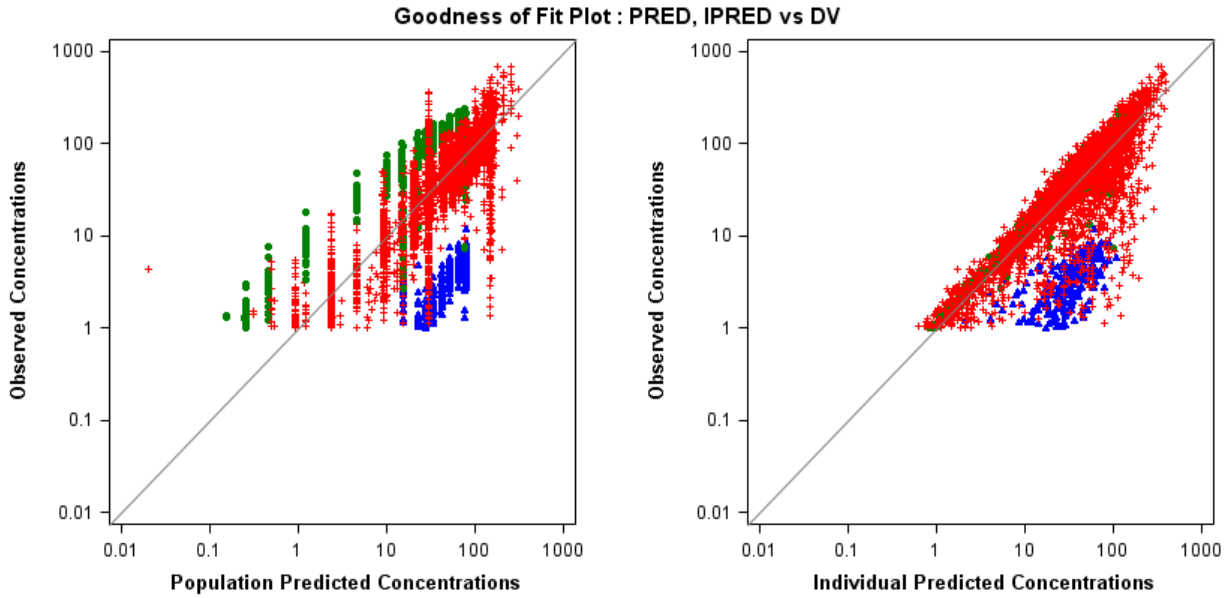
**Data**

The dataset submitted by the sponsor (pkdataset. xpt) was used for the analysis. The analysis was conducted using NONMEM® (Version 7).

**Findings**

Goodness of fit plots for the base model (2 compartment with first order absorption and elimination) are shown in **Figure 14**. The data from rifampicin and clarithromycin study are shown in blue and green colored symbols, respectively. The data from rest of the studies is shown in red colored symbols. If the model were to describe the data reasonably well, the clusters should be distributed around the line of identity (solid black line) as shown in the graph. **Figure 14** suggests that interaction effect should be the covariate that is likely to have the biggest effect on 21-desDFZ pharmacokinetics.

**Figure 14. Goodness-of-Fit for Base Population PK Model for 21-desDFZ. Data shown as blue colored symbols are from rifampicin interaction study. Data shown as green colored symbols are from clarithromycin interaction study. Data shown as red colored symbols are from the other studies.**




Source : Reviewer's Analysis (..\..\..\Data\Def\GoodnessOfFit.sas)

The estimates of pharmacokinetic parameters from the base model are shown in **Table 16** below. These estimates are similar to those reported by the sponsor.

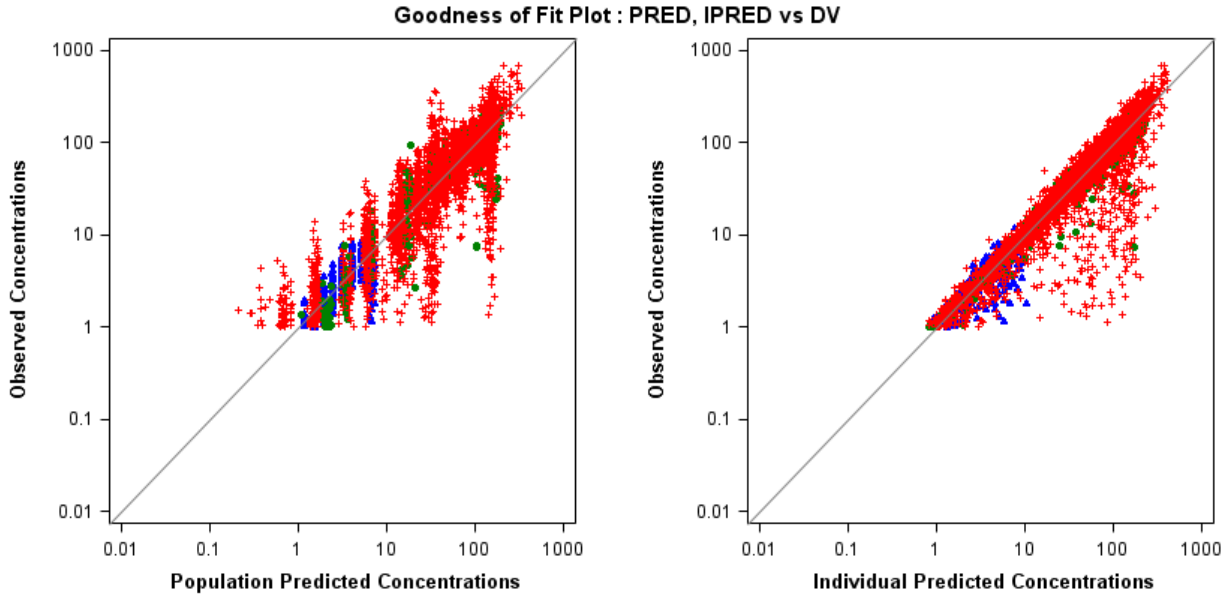
**Table 16. Typical Values of Base Population PK Model for 21-desDFZ**

| Parameter | Typical Value |
|---|---|
| Ka (Absorption rate constant, $hr^{-1}$) | 0.432 |
| Lag time (ALAG, hr) | 0.221 |
| CL/F (Apparent Clearance from Central Compartment, L/hr) | 72.2 |
| Q/F (Distributional Clearance between central and peripheral compartment, L/hr) | 3.84 |
| V/F (Apparent Volume of Distribution of Central Compartment, L) | 13.5 |
| V2/F (Apparent Volume of Distribution of Peripheral Compartment, L) | 35.5 |

Based on the estimated pharmacokinetic parameters in **Table 16**, the half-life ($t_{1/2, beta}$) of 21-desDFZ is about 6.8 h.

The various covariates included in the final population pharmacokinetic model are shown in **Table 12** and **Table 13** except for ALP and PLAT. The goodness of fit plots for the final population pharmacokinetics model are shown in **Figure 15**. Compared to **Figure 14**, the inclusion of various covariates improved the ability of model to better describe the data (as shown by random scatter of individual verus predicted concentrations around the line of identity).

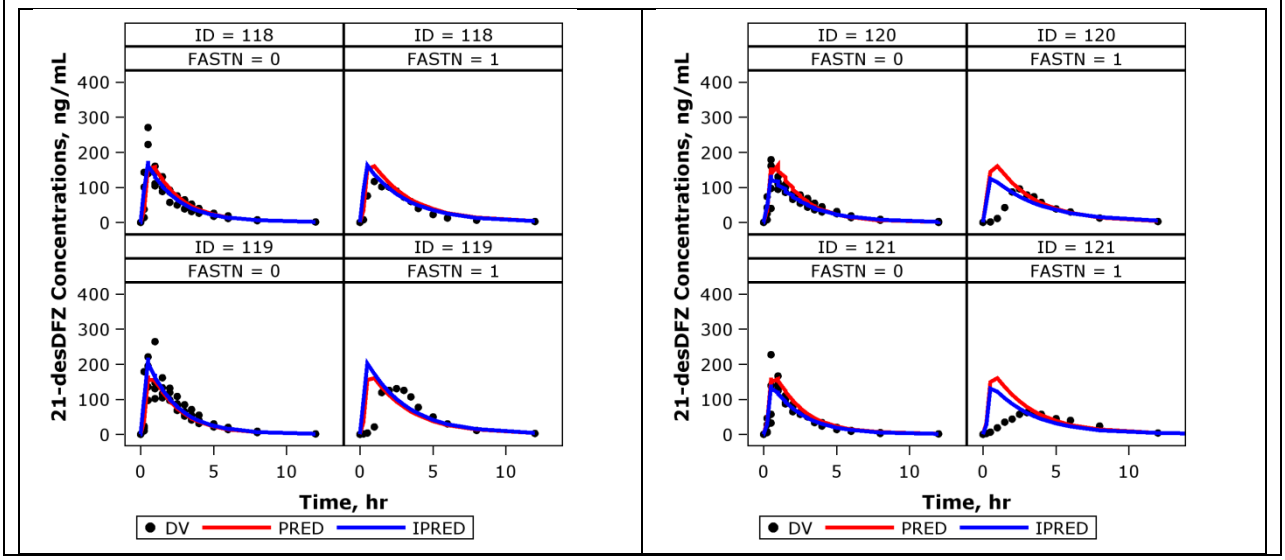
**Figure 15. Goodness-of-Fit of Final Population PK Model for 21-desDFZ covariates. Data shown as blue colored symbols are from rifampicin interaction study. Data shown as green colored symbols are from clarithromycin interaction study. Data shown as red colored symbols are from the other studies.**




Source : Reviewer's Analysis (..\..\..\Data\Def\GoodnessOfFit.sas)

However, over prediction is noted for a cluster of observed concentrations (~1-10 ng/mL). This was examined further using graphical analyses. **Figure 16** shows that in some subjects, high fat meal interferes with the absorption of deflazacort which is reflected in delayed $T_{max}$ of 21-desDFZ. The data suggests that a model with transit compartment would better describe the absorption phase of the concentration-time profile of 21-desDFZ.

**Figure 16. Observed (DV), Population (PRED) and Individual (IPRED) 21-desDFZ Concentrations in Representative Patients Taking Deflazacort With (FASTN=1) and Without High Fat Meal (FASTN=0)**




The parameter estimates from the final population pharmacokinetic model are shown in **Table 17** below.

**Table 17. Typical Values of Final Population PK Model for 21-desDFZ**

| PK Parameters | Typical Value | BSV (%) | Shrinkage (%) |
|---|---|---|---|
| **Ka ($hr^{-1}$)** | 0.491 | 48.37 | 12.06 |
| If High Fat Meal | -0.248* | | |
| Formulation Effect | 0.0298* | | |
| **Frel** | 1 | | |
| If High Fat Meal | 0.298* | 0, FIXED | |
| Formulation Effect | 0.0149* | | |
| **Tlag** | 0.218 | 26.64 | 34.54 |
| **CL/F (L/hr)** | 83.4 | 49.49 | 3.52 |
| With Rifampicin | 1170 | | |
| With Clarithromycin | 24.9 | | |
| If DMD Status | -0.223* | | |
| **CL2/F (L/hr)** | 5.15 | 75.89 | 31.80 |
| **V/F(L)** | 14.6 | 99.74 | 11.36 |
| (WT/70)^ | 0.687 | | |
| If DMD Status | 0.606* | | |
| **V2/F(L)** | 33.5 | 80.06 | 38.05 |
| (WT/70)^ | 0.406 | | |

* Indicates proportional effect. For example a value of -0.248 indicates a decrease by 24.8%

(b) (4) **influence of covariates (body weight, age, gender and race) on 21-desDFZ pharmacokinetics acceptable?**

(b) (4)

**Model based analyses**: Total body weight, age, gender and race were evaluated (individually) for their effect on CL/F, V/F of 21-desDFZ. The evaluation was done after accounting for the effect of rifampicin and clarithromycin on the CL/F of 21-desDFZ. The influence of a covariate on CL/F or V/F would be declared statistically significant ($p \leq 0.05$) if the objective function (-2 log likelihood) decreased by 3.84 points. For the covariate to be declared statistically significant ($p \leq 0.05$) on both CL/F and V/F, the objective function should decrease by 5.99 units. The findings show that covariates such as age, gender and race do not have a significant effect on the pharmacokinetics of 21-desDFZ (**Table 18**) after accounting for body weight effect on CL/F and V/F.

**Table 18. Model Based Evaluation of Influence of Covariates on Apparent Clearance and Volume of Distribution of 21-desDFZ.**

| Covariate | Objective Function (OBJ) | Δ OBJ | Statistically Significant (Yes/No) |
|---|---|---|---|
| Base Model (accounting for rifampicin and clarithromycin effect on CL/F) | 30129 | | |
| Total body weight effect on CL/F and V/F | 30123 | 6 | Yes |
| Age effect on CL/F and V/F | 30120 | 3** | No |
| Gender (Male vs Female) effect on CL/F and V/F | 30123 | 0** | No |
| Race (Caucasian vs Non Caucasian) effect on CL/F and V/F | 30123 | 0** | No |
| ** ΔOBJ value is calculated from the model that included total body weight and the effect of rifampicin, clarithromycin on 21-desDFZ PK. | | | |

**Graphical analyses**:

***Effect of body weight and age on 21-desDFZ pharmacokinetics***

Figure 17 and Figure 18, show the individual level and mean(±SD) concentration-time profile of 21-desDFZ by body weight category and age category, respectively, in DMD patients from Study MP-104-CL-005. Interpretation of the findings being shown in Figure 17 and Figure 18 are provided after Figure 18.

**Figure 17. (Left) Individual Patient-Level 21-desDFZ Plasma Concentrations by Age Category (≤ 11 y and > 11 y). (Right) Mean ±SD 21-desDFZ Concentrations in Patients by Age Category (≤ 11 y and > 11 y)**

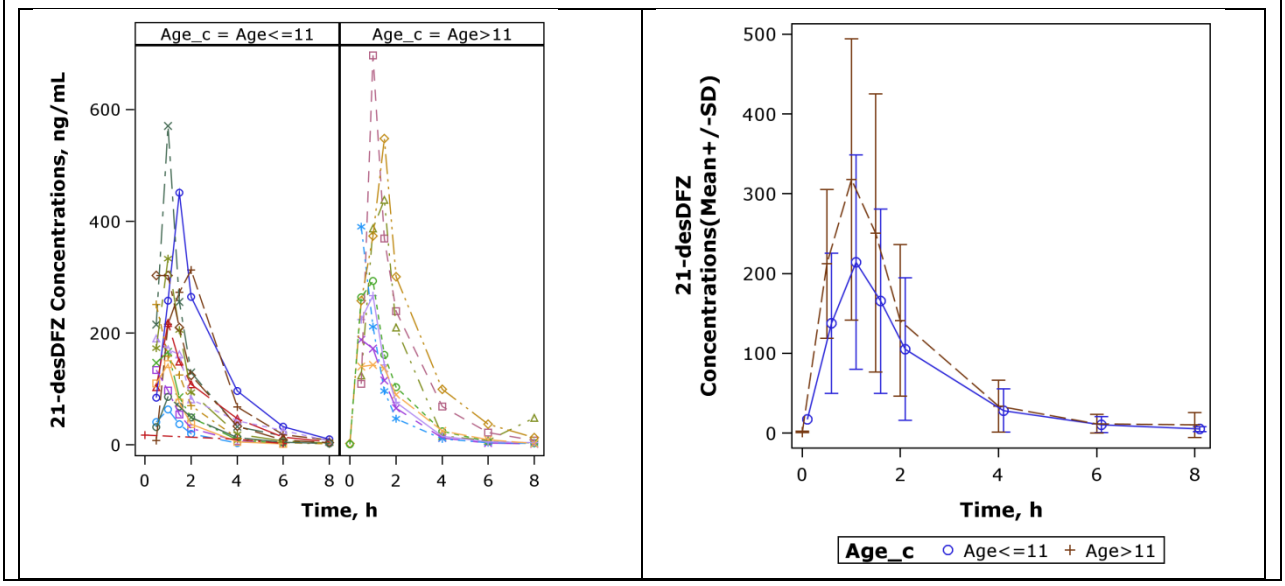
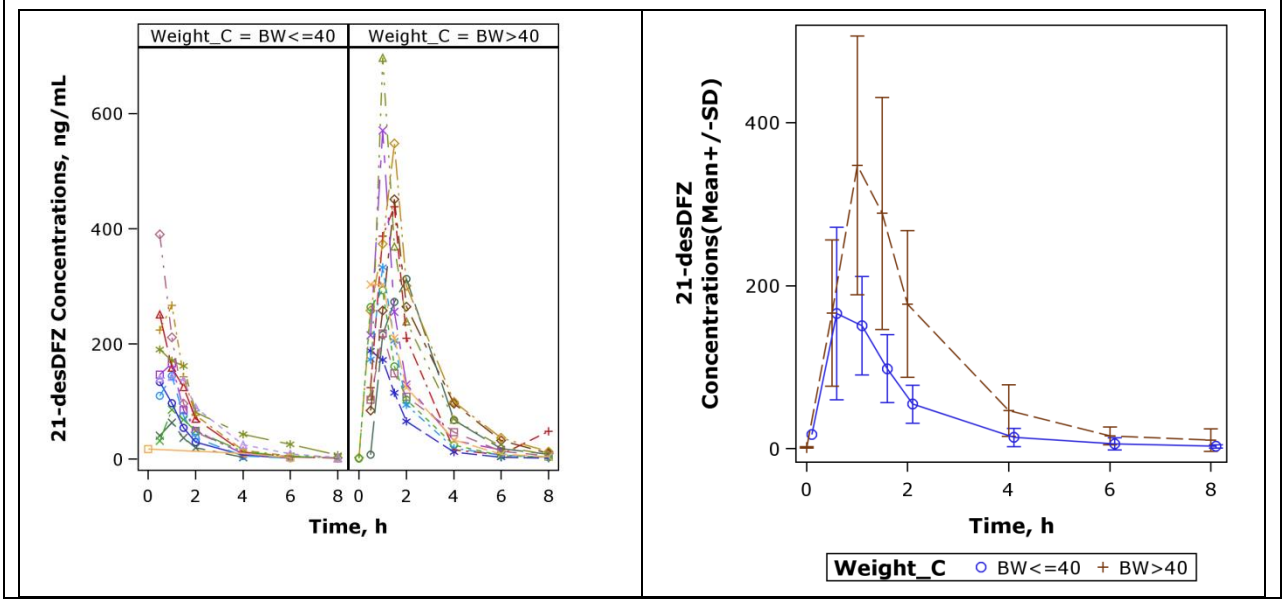


**Figure 18. (Left) Individual Patient-Level 21-DesDFZ Plasma Concentrations by Weight Category (≤ 40 kg and > 40 kg). (Right) Mean ±SD 21-DesDFZ Concentrations in Patients by Weight Category (≤ 40 kg and > 40 kg)**




**Interpretation of the findings as shown in Figure 17 and Figure 18**

Figure 17 shows that the patients whose age is above 11 years have higher average 21-desDFZ concentrations when compared to patients whose age is at or below 11 years. Figure 18 shows that the patients whose body weight is above 40 kg have higher average 21-desDFZ concentrations when compared to patients whose body weight is at or less than 40 kg. These differences are noted from the study where DFZ was administered on a body weight basis (0.9 mg/kg). Per sponsor's calculations, the variability in $C_{max}$ values was larger in children with a geometric CV% of 95.6% compared to 37.7% in adolescents. Consistent with $C_{max}$, the variability in AUC values was larger in children (>85%) than in adolescents (approximately 57%).

The variability in the pharmacokinetics of 21-desDFZ, as shown with individual level data, can be seen in Figure 17 and Figure 18. This variability is unlikely due to the maturation timeline of the enzymes : Esterases that convert deflazacort to 21-desDFZ, CYP3A4 that is responsible for the biotransformation of 21-desDFZ. Figure 17 would suggest that dose adjustments would be needed in one of the age/body weight group to ensure similar 21-desDFZ concentrations across age groups. However, current TREAT-NMD guidelines (http://www.parentprojectmd.org/site/ DocServer/ TREAT-NMD_DMD_interim_ recommendations.pdf) suggest administration of deflazcort on a per kg basis. The

published studies documenting the delayed loss of ambulation by deflazacort also utilized dosing on a per kg basis. Given the extensive prior utilization knowledge of deflazacort in the DMD patients and the lack of exposure-response relationship information for efficacy and safety endpoints, no dosing recommendations are being made that would ensure similar 21-desDFZ concentrations across age/weight groups.

**Effect of gender and race on 21-desDFZ pharmacokinetics**

Figure 19 and Figure 20 show the individual level and mean (±SD) concentration-time profile of 21-desDFZ by race and gender, respectively, in healthy subjects (not taking rifampicin or clarithromycin) and DMD patients.

Interpretation of the findings being shown in Figure 19 and Figure 20 are provided after Figure 20.

**Figure 19. (Left) Individual 21-DesDFZ Plasma Concentrations by Race Category (White=0, Black or African American=1, Asian=2, multiple=3, American Indian or Alaska native=4, and other=9). (Right) Mean ±SD 21-DesDFZ Concentrations by Race Category (Caucasian and Non-Caucasian)**

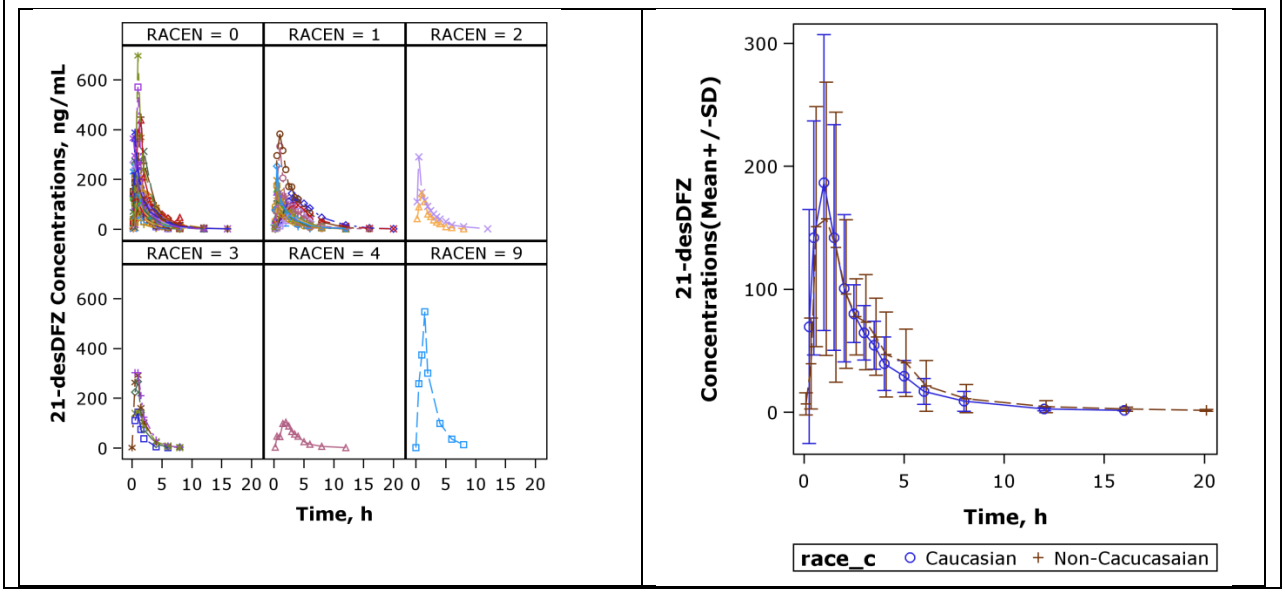
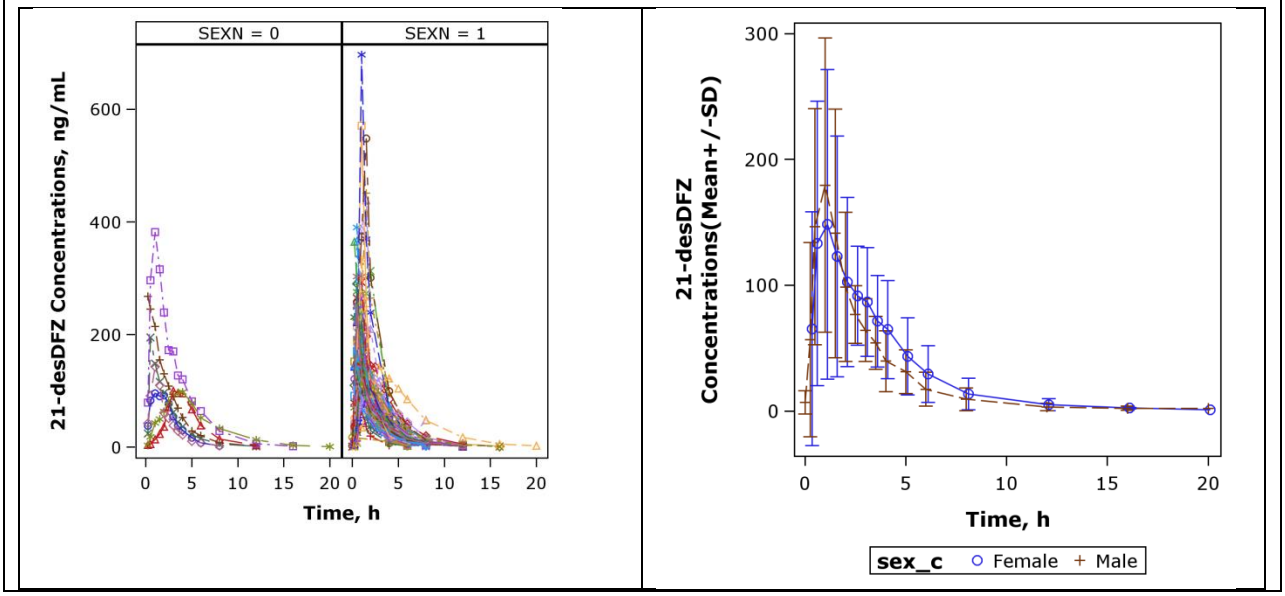



**Figure 20. (Left) Individual Level 21-desDFZ Plasma Concentrations by Sex Category (0- Female, 1-Male). (Right) Mean ±SD 21-desDFZ Concentrations by Sex Category (Male, Female)**




**Interpretation of findings as shown in Figure 19 and Figure 20**

No dose adjustments are needed based on sex or race.

***Comments on the labeling statements proposed by the sponsor***

Overall, the sponsor's proposed labeling statements regarding the influence of age, race and gender on the pharmacokinetics of 21-desDFZ are acceptable with minor changes.

| Proposed by the sponsor<br>In section 12.3 Specific Populations | Suggested revisions by the reviewer |
|---|---|
| (b) (4) | (b) (4)<br>The $C_{max}$ (Mean±SD, N=16) of 21-des DFZ in children (ages (b) (4) 11) and adolescents (ages 12-16) was XXX ng/mL and XXX ng/mL, respectively, on Day 1 after administration of 0.9 mg/kg deflazacort. The AUC0-inf (Mean±SD, N=8) of 21-des DFZ in children (ages (b) (4) 11) and adolescents (ages 12-16) was XXX ng•h/mL and XXX ng•h/mL on Day 1 after administration of 0.9 mg/kg deflazacort.<br>(b) (4) |
| There are no differences in the pharmacokinetics of 21-desDFZ between males and females.<br><br>*Race/Ethnicity* | There are no differences in the pharmacokinetics of 21-desDFZ between males and females.<br><br>*Race/Ethnicity* |
| (b) (4) | There are no differences in the pharmacokinetics of 21-desDFZ between Caucasians and non-Caucasians. |

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### 4.10 Relative BA/BE and Food Effect Study

| **Study report:** MP-104-CL-026 | **Study period:** June – August, 2015 | EDR Link[2] |
|---|---|---|

**Title of the study:** A Single-Dose, Single-Center, Randomized, Five Period Crossover Study Comparing Food Effect And Bioavailability Of Deflazacort Formulations In Healthy Volunteers

**Objectives:**

- To assess the comparative bioavailability of the commercial formulation of deflazacort 36 mg tablets (1 × 36 mg) compared to an investigational tablet formulation (6 × 6 mg) used in previously conducted clinical pharmacology studies
- To evaluate the effect of food on the pharmacokinetics (PK) of a single oral dose of the commercial (1 × 36 mg) tablets
- To assess the comparative bioavailability of crushed tablets (commercial formulation, 1 × 36 mg) in applesauce versus an intact tablet (commercial formulation, 1 × 36 mg)
- To assess the comparative bioavailability of oral suspension (36 mg/1.58 mL) in apple juice versus an intact tablet (commercial formulation, 1 × 36 mg)
- To assess the safety of deflazacort when administered as single 36-mg doses under various conditions (fasted, fed, as crushed tablet, intact tablet, and oral suspension)

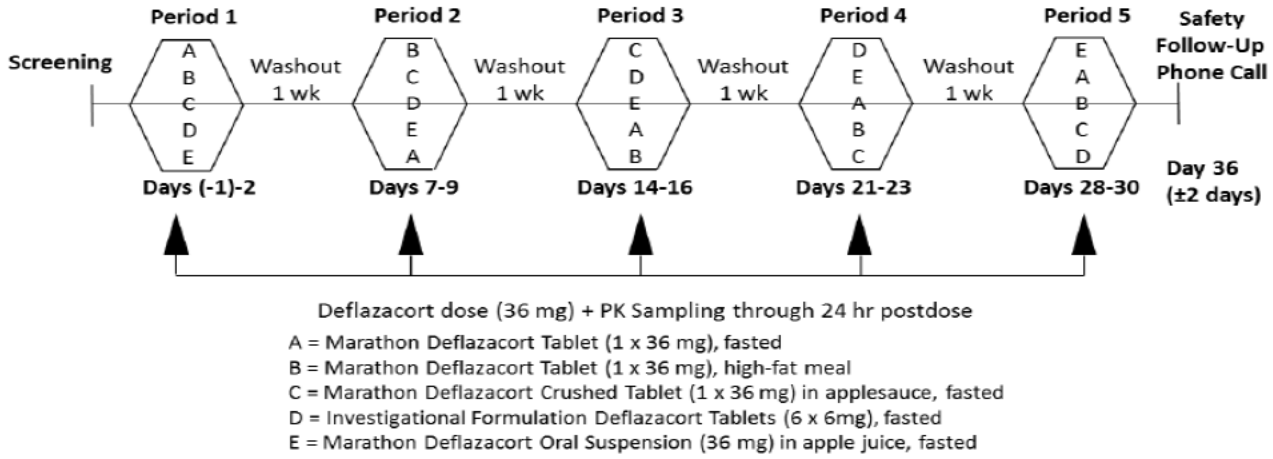
**Study Design**

This was a Phase 1, single-center, single-dose, randomized, 5-period crossover study. 45 subjects were randomly assigned to 1 of 5 treatment sequences. Each dosing sequence was enrolled in parallel and received all 5 treatments in a crossover fashion Figure 23.

Subjects were screened within 28 days of the first dose of study drug. Subjects checked into the unit on the day prior to dosing (Day -1 for Period 1) and stayed in house through the 24 hour assessments in each study period. Safety assessments were performed at screening, check-in for each period, and at 24 hours after each dose per the Schedule of Assessments. Additionally, a safety follow-up phone call was performed on Day 36 (± 2 days).

*Reviewer's Comments: The treatment E, oral suspension vs. tablets is the pivotal BE study that supports NDA* 208685 *for the suspension formulation. OSIS inspection report for this part of the study is currently pending.*

**Figure 23: Study MP-104-CL-026 Design Schematic**




Source: Study report: MP-104-CL-026, Page 16 of 243, Figure 1

**PK Sampling**

Blood samples were collected after each treatment period at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 20, 24 hours post dose.

**Statistical Method**

Comparative bioavailability assessment was performed using a standard bioequivalence approach using a two-one sided test approach. Natural-log-transformed $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ values were used to calculate ratios and construct confidence intervals. Analyses were conducted using the average bioequivalence approach and involved the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures: Test versus Reference treatment.

To establish bioequivalence, the calculated confidence interval should fall within the accepted a bioequivalence limit, 80% to 125% for the ratio of the product averages. A Wilcoxon test was used to assess the differences in $t_{max}$ between treatments, and a Hodges Lehman estimation was used to describe the confidence interval around the median $t_{max}$.

**Population and Disposition**

- Healthy male and female subjects between the ages of 19 and 55 years, inclusive, at the time of screening with a body mass index of 18 to 32 kg/m², inclusive, at screening and Day -1.
- 45 subjects were planned to be enrolled in this study. 40 subjects completed the sutudy.

  5 subjects discontinued; 1 subject was discontinued by the investigator because of compliance issues, 3 subjects were discontinued due to protocol deviations, and 1 subject withdrew from the study.

**Results**

Deflazacort is rapidly converted by plasma esterase to 21-desDFZ and intact deflazacort was not detected in the plasma. Only 21-DesDFZ was be analyzed and used in the statistical analysis.

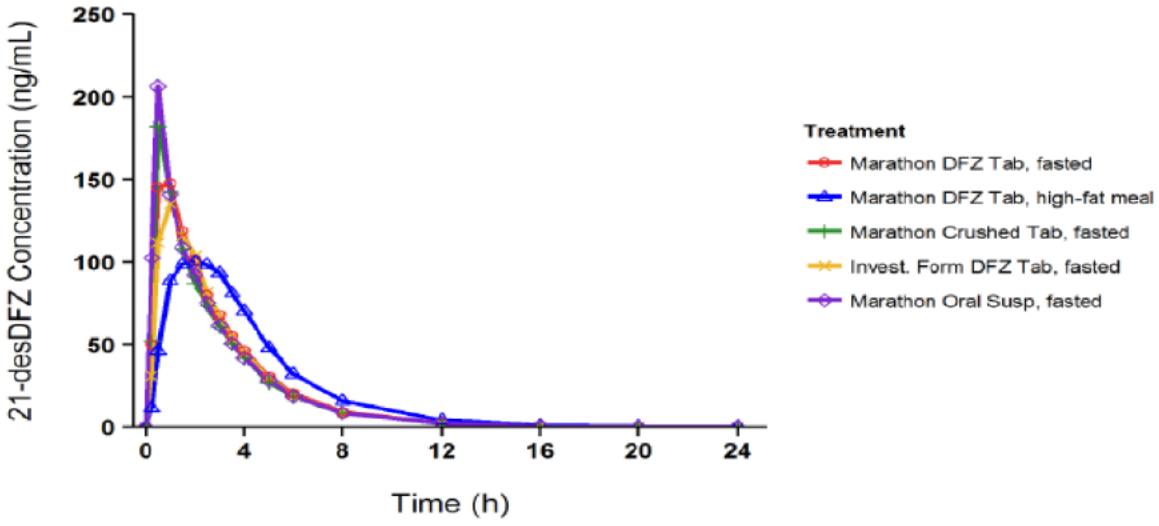
The mean plasma concentrations for the different treatments are overlaid in Figure 24.

Oral suspension, crushed tablet and investigational tablet formulations were comparable as assessed by the AUC and $C_{max}$ ratios.

The 90% confidence interval for the AUC and $C_{max}$ ratios was within 80 – 125% **Table 21**.

Comparison of the effect of food (high-fat diet vs fasted) on the PK of a single oral dose of deflazacort showed that the extent of exposure (as assessed by AUC) was similar in fed and fasted conditions. However, with a high-fat meal, $C_{max}$ was reduced and $T_{max}$ was delayed by one hour relative to administration under fasting conditions. This indicate lower rate of absorption associated with the administration of deflazacort with food.

**Figure 24 Mean Plasma 21-desDFZ Concentration vs Time profile.**




Source: Study report CL-026, Figure.2, Page 34/243

**Table 21 Relative Bioavailability and Food Effect Results for Deflazacort**

| PK Parameter | % Ratio Relative to Marathon Commercial Formulation (Fasted) | 90% Confidence Interval |
|---|---|---|
| **Marathon Deflazacort Tablet High Fat Meal** | | |
| **Ln(AUCINF obs)** | 110.8 | 106.3-115.4 |
| **Ln(AUC-last)** | 111.2 | 106.7-115.9 |
| **Ln($C_{max}$)** | 71.8 | 65.1-79.2 |
| **Marathon Crushed Tablet (Fasted)** | | |
| **Ln(AUCINF obs)** | 97.3 | 93.4-101.3 |
| **Ln(AUC-last)** | 97.3 | 93.3-101.4 |
| **Ln($C_{max}$)** | 100.9 | 91.5-111.3 |
| **Investigational Formulation (Fasted)** | | |
| **Ln(AUCINF obs)** | 94.6 | 91-98.6 |
| **Ln(AUC-last)** | 94.8 | 91.0-98.8 |
| **Ln($C_{max}$)** | 85.7 | 77.7-94.4 |
| **Marathon Oral Suspension (Fasted)** | | |
| **Ln(AUCINF obs)** | 102.3 | 98.3-106.6 |
| **Ln(AUC-last)** | 102.7 | 98.5-107.0 |
| **Ln($C_{max}$)** | 110.5 | 100.2-121.9 |

Source: Table generated by FDA from Data file **[**\\cdsesub1\evsprod\nda208684\0000\m5\datasets\mp-104-cl-026\analysis\programs\pc.sas7bdat]

**Bio-Analytical Assay and Sample Analysis**

| | 21-DesDFZ |
|---|---|
| **Method** | **UPLC-MS/MS** |
| LLOQ (ng/mL) | 1.0 |
| Range (pg/mL) | 1.0 to 200 |
| Accuracy/Bias | 96.7 % to 104.5 % |
| Precision | 3.5 % to 6.5 % |

*Reviewer's Comments:*

*The overall study design is acceptable. The analytical assay method and sample analysis is also acceptable.*

**Safety**

There were no deaths, serious AEs (SAEs), or AEs which led to discontinuation.

**SUMMARY**

- The commercial tablet formulation is bioequivalent to oral suspension formulation, crushed tablets and investigational deflazacort formulation under fasted condition.
- Comparison of the effect of food (high-fat diet vs fasted) on the PK of a single oral dose of the commercial tablets showed that AUC was comparable under fasting conditions and with a high-fat meal.
- Administration of commercial tablets with a high-fat meal reduced $C_{max}$ by 30% and delayed $t_{max}$ by one hour relative to administration under fasting conditions, indicating lower rate of absorption associated with administration of deflazacort with food.
- The OSIS inspection report for treatment E that compares oral suspension with oral tablets is currently pending. This study supports NDA 208685 for the deflazacort oral suspension formulation.

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/s/

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