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Delayed-Release Dimethyl Fumarate Does Not Adversely Affect the Pharmacokinetics of a Commonly Used Oral Contraceptive (Norgestimate/Ethinyl Estradiol) in Healthy Women: Drug-Drug Interaction Study Results

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INTRODUCTION

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated significant efficacy and a favorable benefit-risk profile in relapsing-remitting multiple sclerosis (RRMS) in clinical trials.[1,2]
- As women of childbearing age comprise a large proportion of the MS population, it is important to study potential drug-drug interactions between MS disease-modifying therapies and oral contraceptives (OC).
- The purpose of this study was to evaluate the effect of DMF (240 mg twice daily [BID]) on the pharmacokinetics (PK) of a commonly administered OC, Ortho-Cyclen (250 mcg norgestimate, 35 mcg ethinyl estradiol).

OBJECTIVES

- The primary objective was to assess the effect of DMF on the PK of norgestimate (via levels of norelgestromin, the primary metabolite of norgestimate) and ethinyl estradiol in healthy female volunteers.
- Secondary objectives were to describe the effect of DMF on the pharmacodynamics (PD) of OC (via serum progesterone levels) and characterize the safety and tolerability of DMF when coadministered with OC.
- An exploratory objective was to assess the PK of DMF when coadministered with OC (via levels of monomethyl fumarate, the main metabolite of DMF [MMF]).

METHODS

Participants and Study Design

- In this open-label, randomized, 2-way crossover study (Figure 1), eligible participants were healthy women of childbearing potential (age, 18–45 years; body mass index [BMI], 19.0–30.0 kg/m^2).
- All participants received OC on Days 1–28 of the Lead-in Period.
  - Participants with progesterone levels ≥3 ng/mL on Days 21 or 22 of the Lead-in Period did not continue in the study.
- On Day 28 of the Lead-in Period, eligible participants were randomized 1:1 to 1 of 2 treatment sequences:
  - In sequence 1, participants received OC coadministered with DMF in Period 1, then OC alone in Period 2
  - In sequence 2, these regimens were reversed.
- Each Period was 28 days in duration.

Dosing

- OC was administered once daily on Days 1–28 of each Period. A 28-day supply of OC included 21 active tablets (250 mcg norgestimate, 35 mcg ethinyl estradiol; administered on Days 1–21) and 7 inactive tablets (administered on Days 22–28).
- DMF was dosed at 240 mg BID and administered only for the first 21 days when applicable.

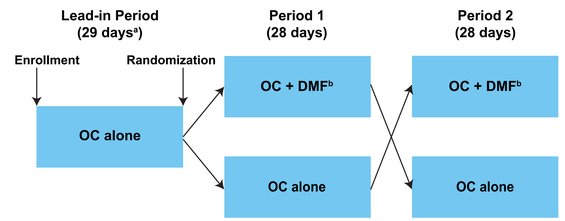
PK and PD Sampling Schemes

- Blood samples for the PK analysis of norelgestromin and ethinyl estradiol were collected pre dose on Day 21 of each Period and at multiple time points (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours) post dose.
- Blood samples for the PK analysis of DMF (as measured by MMF concentrations) were collected during the Period in which DMF was administered, pre dose and at multiple time points (0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hours) post first dose of the day.
- For PD analyses, blood samples were collected on Days 14, 21, 22, and 28 of each treatment period.

Statistical Analysis

- To analyze the log-transformed primary PK endpoints area under the plasma concentration-time curve over the dosing interval ($AUC_{0-\tau}$) and peak plasma concentration (C_{max}), statistical analysis was performed using a mixed-effects analysis of variance model including treatment, sequence, and period as fixed effects and subject as random effect.

Figure 1. Study design



[a]Includes Day –1
[b]DMF, delayed-release DMF (also known as gastro-resistant DMF)

RESULTS

Participants

- A total of 46 women were enrolled, 41 were randomized, 40 were dosed, 32 completed the study, and 10 withdrew due to adverse events (AEs).
- Mean (SD) age of enrolled participants was 31.2 (6.7) years and mean (SD) BMI was 25.7 (2.6) kg/m^2.

PK of Norelgestromin, Ethinyl Estradiol, and DMF

- Mean plasma norelgestromin and ethinyl estradiol concentration profiles were superimposable following OC alone and OC coadministered with DMF (Figure 2).
- PK parameters are summarized in Table 1. There was no statistically significant effect of DMF on the PK parameters of norelgestromin and ethinyl estradiol, with 90% CIs of geometric mean ratios for $AUC_{0-\tau}$ and C_{max} contained within the 0.8–1.25 range.
- DMF was rapidly absorbed following oral administration, with C_{max} achieved at median time to peak plasma concentration (T_{max}) of 2.33 hours post dose (ranging from 1.0 to 6.1 hours post dose). After reaching C_{max}, plasma MMF concentrations declined rapidly with a short mean half-life ($t_{1/2}$) of 0.72 hours. The mean C_{max} and AUC from time zero to infinity ($AUC_{0-\infty}$) values were 2357 ng/mL and 3811 h*ng/mL, respectively.

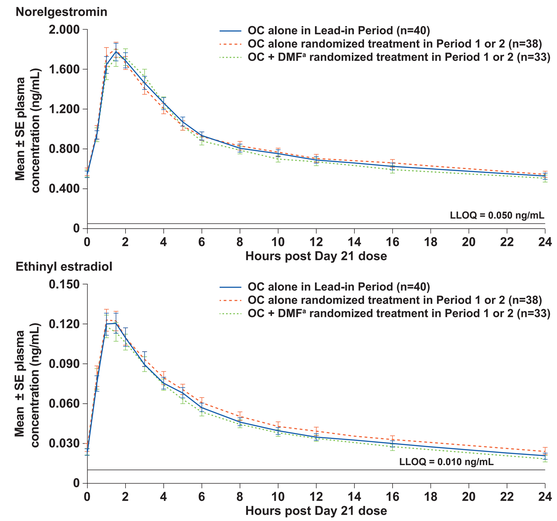
Serum Progesterone Levels

- Median serum progesterone levels were comparable across the time points assessed and were comparable following OC alone in the Lead-in Period, OC alone (randomized), and OC coadministered with DMF, with values on Day 21 of 0.325, 0.410, and 0.330 ng/mL, respectively.

Safety

- A summary of treatment-emergent AEs (TEAEs) is presented in Table 2.
  - The majority of TEAEs were considered to be mild.
- The most frequently experienced TEAE was flushing. All flushing events occurred during coadministration of OC and DMF (18 participants; 46%).
- Gastrointestinal disorders was the most frequently reported System Organ Class, with nausea and vomiting most frequently experienced. These events mostly occurred during coadministration of OC and DMF (nausea, 10 participants [26%]; vomiting, 9 participants [23%]).

Figure 2. Mean ± SE plasma norelgestromin and ethinyl estradiol concentrations over time



LLOQ = lower limit of quantification
[a]DMF, delayed-release DMF (also known as gastro-resistant DMF)

Table 1. Summary of plasma norelgestromin and ethinyl estradiol PK parameters

	OC alone randomized treatment[a]	OC coadministered with DMF[a,b]	Estimated geometric mean ratio (90% CI)[c]
No. of participants	**39**	**39**	**–**
Norelgestromin			
$AUC_{0-\tau}$ (h*ng/mL)	19.884 ± 5.864	19.057 ± 5.104	0.975 (0.923–1.030)
C_{max} (ng/mL)	1.926 ± 0.481	1.889 ± 0.450	0.990 (0.921–1.063)
T_{max} (h)	1.5 ± 0.6	1.9 ± 0.7	–
$t_{1/2}$ (h)	15.6 ± 0.7	13.6 ± 3.2	–
Ethinyl estradiol			
$AUC_{0-\tau}$ (h*ng/mL)	1.180 ± 0.502	1.050 ± 0.403	0.937 (0.888–0.988)
C_{max} (ng/mL)	0.132 ± 0.052	0.123 ± 0.047	0.972 (0.825–1.119)
T_{max} (h)	1.3 ± 0.4	1.3 ± 0.4	–
$t_{1/2}$ (h)	11.8 ± 2.6	11.1 ± 2.2	–

[a]Values are mean ± SD
[b]DMF, delayed-release DMF (also known as gastro-resistant DMF)
[c]OC coadministered with DMF/OC alone

Table 2. Overall summary of TEAEs

n (%)	OC alone in Lead-in Period	OC alone randomized treatment	OC coadministered with DMF[a]	Overall
Dosed	**46 (100)**	**39 (100)**	**39 (100)**	**46 (100)**
Any AE[b]	**19 (41)**	**10 (26)**	**26 (67)**	**31 (67)**
Mild	16 (35)	9 (23)	25 (64)	26 (57)
Moderate	2 (4)	1 (3)	1 (3)	4 (9)
Severe	1 (2)[c]	0	0	1 (2)[c]
SAE	**1 (2)[c]**	**0**	**0**	**1 (2)[c]**
Discontinuation due to AE	**2 (4)**	**3 (8)**	**6 (15)**	**10 (22)**
Death	**0**	**0**	**0**	**0**

SAE = serious adverse event
[a]DMF, delayed-release DMF (also known as gastro-resistant DMF)
[b]TEAEs were defined as AEs that: (1) started on or after the dosing of study treatment or (2) were present before the dosing of study treatment and subsequently worsened in severity after receiving study treatment
[c]One participant experienced a severe AE of pulmonary embolism during the Lead-in Period, which was reported as an SAE. This event was considered to be related to OC and led to withdrawal of the participant from the study

CONCLUSIONS

- DMF coadministered with an OC containing norgestimate and ethinyl estradiol did not change the PK or PD characteristics of the OC.
- The safety profile of DMF coadministered with OC was consistent with the known safety profile of DMF.
- The PK profile of DMF coadministered with OC was consistent with the known PK profile of DMF alone.
- These results suggest that women of childbearing potential treated with DMF are able to use a combined OC for contraception without dose modification. No impact on the PK of MMF was seen with the concomitant use of OCs.

References

1. Gold R, *et al.*; DEFINE Study Investigators. *N Engl J Med.* 2012;367(12):1098-1107.
2. Fox RJ, *et al.*; CONFIRM Study Investigators. *N Engl J Med.* 2012;367(12):1087-1097.

Disclosures

BZ, IN, GZ, VM, and SIS: employees of and stockholders in Biogen; JK: employee of Covance Inc.

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