**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.

- 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 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 (n = 41) were randomized to 1 of 2 treatment 
  sequences for the PK analysis of norelgestromin and ethinyl 
  estradiol.

Methods

- 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 (5.7) kg/m^2.

- PNK 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-τ over 0.8 to 1.2.

- 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 1.6 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.

- 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.

**RESULTS**

- 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 under the 
  plasma concentration-time curve over the dosing interval 
  (AUC_{0-τ}) and peak plasma concentration (C_{max}), a 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

<table>
<thead>
<tr>
<th>Lead-in Period</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1–28</td>
<td>OC alone</td>
<td>OC + DMF</td>
</tr>
<tr>
<td>Days 21–22</td>
<td>OC alone</td>
<td>OC alone</td>
</tr>
<tr>
<td>Days 21–22</td>
<td>OC alone</td>
<td>OC alone</td>
</tr>
</tbody>
</table>

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

- 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%]).

**CONCLUSIONS**

- DMF coadministered with 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 monotherapy 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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of participants</th>
<th>OC alone (control)</th>
<th>OC alone and DMF</th>
<th>Estimated geometric ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norelgestromin</td>
<td>39</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmin (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>29</td>
<td>29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Overall summary of TEAEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients</th>
<th>OC alone (Control)</th>
<th>OC alone and DMF</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Discontinuation due to AE</td>
<td>2</td>
<td>3 (8)</td>
<td>6 (15)</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DMF delayed-release DMF (also known as gastro-resistant DMF)</td>
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</table>

**ACKNOWLEDGMENTS**

This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for this manuscript was provided by Biogen.

**REFERENCES**