Efficacy of Delayed-release Dimethyl Fumarate in Newly Diagnosed Patients With Relapsing-remitting Multiple Sclerosis Using a Composite Measure of Disability: Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies

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Introduction

- Newly diagnosed patients with RRMS may have better long-term outcomes if treated early with a therapy that controls their disease activity.
- As previously reported, the estimated proportion of newly diagnosed patients in DEFINE/CONFIRM with 12-week confirmed EDSS progression at 2 years was 23% in the PBO group and 7% in the DMF 240 mg BID group, representing a relative risk reduction of 71% (p < .0001 vs. PBO).

Disclosures and Acknowledgments

• Disclosures
  - J. Theodore Phillips: consultant fees from Acorda, Biogen, Genentech, Merck Serono, Sanofi-Genzyme, and Xenoport
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**Study Design**

**DEFINE/CONFIRM**

- Inclusion criteria included:
  - Age: 18–55 years
  - Diagnosis of RRMS (McDonald criteria)
  - EDSS score of 0–5.0
  - ≥1 relapse in the 12 months before randomization OR ≥1 Gd+ lesion in the 6 weeks before randomization

- Exclusion criteria included:
  - Prior treatment with GA within the past 3 months (DEFINE) or at any time (CONFIRM)

- Newly diagnosed patients were defined as:
  - RRMS diagnosed within 1 year before the study entry AND
  - Naïve to MS disease-modifying therapy or previously treated with corticosteroids alone

**Methods**

- Composite-confirmed disability progression (CDP) was defined as the first occurrence of sustained worsening from baseline of any of the following components:
  - EDSS
  - Timed 25-Foot Walk (T25FW)
  - 9-Hole Peg Test (9HPT)
  - Paced Auditory Serial Addition Test (PASAT)
  - Visual Function Test (VFT)

- Assessments were performed at baseline and at 12-week intervals thereafter

- Composite-CDP was confirmed for 12 or 24 weeks by assessing any of the functional outcomes

- Statistical analysis comparisons were based on a Cox proportional hazards model adjusted for baseline covariates

- Results are reported for PBO and DMF 240 mg BID (the approved dosage)

- The GA arm was excluded from the analysis of newly diagnosed patients in DEFINE/CONFIRM (and from all other integrated analyses of DEFINE/CONFIRM), as it was a reference arm and was included in CONFIRM only

**Baseline Demographics and Disease Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n=223</th>
<th>DMF BID n=221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.5 (9.4)</td>
<td>35.3 (9.4)</td>
</tr>
<tr>
<td>Female, %</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Time since first MS symptoms, y</td>
<td>4.3 (5.3)</td>
<td>4.3 (5.8)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>2.0 (0, 31)</td>
<td>2.0 (0, 42)</td>
</tr>
<tr>
<td>Time since diagnosis, y</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>1.0 (0, 1.0)</td>
<td>1.0 (0, 1.0)</td>
</tr>
<tr>
<td>Relapses in prior year</td>
<td>1.4 (0.6)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>Prior treatment with steroids, %</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.2 (1.1)</td>
<td>2.1 (1.1)</td>
</tr>
</tbody>
</table>

*Values are mean (SD), unless stated otherwise. "DMF" = delayed-release DMF (also known as gastro-resistant DMF); max = maximum; min = minimum. 1. Gold R, et al. Mult Scler. 2015;21(1):157–66.
Conclusions

- DMF 240 mg BID significantly reduced the risk of CDP in newly diagnosed patients with RRMS compared with PBO as measured using functional composite endpoints
  - Statistically significant reductions for DMF vs. PBO also were observed across all combinations of the EDSS plus each of the other individual components
  - These findings are consistent with previously published data suggesting the potential for greater clinical benefits in patients with RRMS who receive DMF treatment early in their disease course
  - Although this analysis presents its own limitations (e.g. patients with worsening in one component were treated the same as those with worsening in multiple components), the composite CDP measure proposed here may be more reliable than assessing its individual components alone, capturing clinically meaningful changes in disability progression across multiple neuro-performance components