Fingolimod by Prior Efficiency: Disease-Modifying Therapy Experience: FREEDOMS


London Health Sciences Centre, London, ON, Canada; St. Michael's Hospital, Toronto, ON, Canada; Institut für Münchener Neuroimmunologie, Munich, Germany; University Hospital, Basel, Switzerland; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

INTRODUCTION AND PURPOSE

• In patients with multiple sclerosis (MS), use of disease-modifying therapy (DMT) is variable and dynamic, with substantial proportions of patients not being treated with DMT or stopping or switching DMT, often because of adverse events (AEs) or inadequate efficacy.

Fingolimod is a sphingosine 1-phosphate receptor modulator and is the only once-daily medication approved in the United States for a treatment for relapsing forms of MS.

In the 2-year phase 3 Fingolimod Research Evaluating Effects of Oral Therapy in Multiple Sclerosis (FREEDOMS) study, once-daily fingolimod reduced the annualized relapse rate (ARR) by 0.39% compared with patients receiving fingolimod 0.5 mg (Table 3), 1.25 mg (0.32), 1.0 mg (0.49), and placebo (0.40) for both-eyes-dosed patients.

A post-hoc analysis of FREEDOMS was conducted to determine whether fingolimod efficacy is consistent across patient subgroups defined by MS history.

• Efficacy results based on duration of previous DMT.

METHODS

Study design and patients

FREEDOMS was a phase 3, randomized, double-blind study of fingolimod 0.5 mg or 1.25 mg as a placebo once daily for 2 years.

Patients were aged 18–55 years, with a diagnosis of relapsing-remitting MS according to the revised McDonald criteria, a score of 0.5–5.5 on the Expanded Disability Status Scale (EDSS), and relapse in the previous 12 months in the previous 2 years.

Patients who previously received interferon or glatiramer acetate were required to discontinue therapy by their own choice 3 months before randomization.

Figure 1. FREEDOMS study design

Randomization

Core phase

Extension study

Analysis

• ARR was defined as the number of confirmed relapses per year and was measured in the following subgroups:
  - Patients defined by duration of prior DMT (≤ 1, >1-3 years, >3 years)
  - Patients who discontinued prior DMT owing to AEs
  - Patients who discontinued prior DMT owing to unsatisfactory therapeutic effect

• Statistical analyses were conducted in the intent-to-treat population using a negative binomial regression model adjusted for treatment, subgroup, and treatment-by-subgroup interaction.

RESULTS

Efficacy based on duration of previous DMT

• The proportion of patients (90%) who were on DMT 1.34% had a previous DMT duration < 1 year, 12.5% had a previous DMT duration of 1–3 years, 12.5% had a previous DMT duration of 4–9 years, and 10.7% had a previous DMT duration > 9 years.

• Baseline demographic and clinical characteristics by duration of previous DMT are shown in Table 1.

• Fingolimod 1.25 mg significantly reduced the ARR compared with placebo (Table 3).

Efficacy in patients with prior DMT discontinuation owing to AEs

• In patients who discontinued prior DMT owing to unsatisfactory therapeutic effect, the ARR was significantly reduced by both doses of fingolimod in placebo–treated patients (Table 3).

Table 3. Efficacy result based on duration of previous DMT (randomized population)

<table>
<thead>
<tr>
<th>Duration of previous DMT</th>
<th>Placebo</th>
<th>Fingolimod 0.5 mg</th>
<th>Fingolimod 1.25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 9 years</td>
<td>28.9 (8)</td>
<td>13.4 (8)</td>
<td>10.7 (8)</td>
</tr>
<tr>
<td>4–9 years</td>
<td>23.2 (12)</td>
<td>10.9 (12)</td>
<td>12.5 (12)</td>
</tr>
<tr>
<td>1–3 years</td>
<td>21.5 (16)</td>
<td>12.5 (16)</td>
<td>12.5 (16)</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>26.8 (16)</td>
<td>12.5 (16)</td>
<td>12.5 (16)</td>
</tr>
</tbody>
</table>

Table 4. Demographic and clinical characteristics by duration of previous DMT (randomized population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prior DMT duration ≤ 1 year</th>
<th>Prior DMT duration 1–3 years</th>
<th>Prior DMT duration 4–9 years</th>
<th>Prior DMT duration &gt; 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.5 (12) (243)</td>
<td>46.5 (12) (243)</td>
<td>46.2 (12) (243)</td>
<td>46.4 (12) (243)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>54.1 (12) (243)</td>
<td>50.0 (12) (243)</td>
<td>50.0 (12) (243)</td>
<td>50.0 (12) (243)</td>
</tr>
<tr>
<td>Duration (EDSS)</td>
<td>5.0 (12) (243)</td>
<td>4.9 (12) (243)</td>
<td>4.8 (12) (243)</td>
<td>4.8 (12) (243)</td>
</tr>
<tr>
<td>Relapses in previous 1 y</td>
<td>15.0 (12) (243)</td>
<td>15.0 (12) (243)</td>
<td>15.0 (12) (243)</td>
<td>15.0 (12) (243)</td>
</tr>
<tr>
<td>EDSS scores</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
</tr>
<tr>
<td>EDSS baseline score</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
<td>2.0 (12) (243)</td>
</tr>
<tr>
<td>MIRV volume</td>
<td>51 (7621) (363)</td>
<td>50 (7621) (363)</td>
<td>50 (7621) (363)</td>
<td>50 (7621) (363)</td>
</tr>
<tr>
<td>MIRV baseline</td>
<td>50 (7621) (363)</td>
<td>50 (7621) (363)</td>
<td>50 (7621) (363)</td>
<td>50 (7621) (363)</td>
</tr>
<tr>
<td>MIRV change</td>
<td>(972) (363) (7621)</td>
<td>(972) (363) (7621)</td>
<td>(972) (363) (7621)</td>
<td>(972) (363) (7621)</td>
</tr>
</tbody>
</table>

Table 5. Efficacy result based on duration of previous DMT (randomized population)

| Table 5. Efficacy result based on duration of previous DMT (randomized population)

CONCLUSIONS

• Results of these phase 3 subgroup analyses are consistent with the overall population results in demonstrating a significant reduction in ARR with fingolimod vs placebo.

• Fingolimod was effective in reducing the ARR regardless of duration of prior DMT and in patients who discontinued prior DMT owing to AEs, as well as in those who discontinued prior DMT owing to unsatisfactory therapeutic effect.

• These analyses demonstrate broad clinical efficacy and support the conclusion that fingolimod can benefit treatment-naive patients as well as patients with a long history of prior treatment, including those in whom previous DMT failed or was poorly tolerated.

REFERENCES


5. The authors would like to thank Mucin, MCSTR and the authors for their contributions to this paper. Editorial support was provided by Cognitive Healthcare Communications, Chicago, IL. Medical writing and editorial support was funded by Novartis Pharmaceuticals Corporation.