CONCLUSIONS

• In the phase 3, placebo-controlled FREEDOMS II trial of fingolimod in patients with RRMS, estimates of PBVC obtained using Bayesian power prior methodology were consistent with previously reported results in phase 3 fingolimod studies.

• Application of Bayesian methodology may improve estimates of treatment effects and their interpretability.

OBJECTIVE

• To estimate PBVC in patients with RRMS treated with fingolimod in FREEDOMS II using Bayesian power prior methodology.

METHODS

Study designs and participants

• FREEDOMS and FREEDOMS II included patients aged 18–55 years with a diagnosis of RRMS defined using the 2005 revised McDonald criteria, who experienced at least one confirmed relapse in the previous year or at least two in the previous 2 years and who had an Expanded Disability Status Scale (EDSS) score of 0–5.5 at enrollment.

• Percentage BV change (PBVC), a BV parameter commonly reported in clinical trials, was calculated over the course of the primary studies.

• More sensitive estimates of the effect of fingolimod on PBVC may be obtained with Bayesian methodology, using prior evidence (FREEDOMS) to analyze FREEDOMS II data with probabilistic interpretation.

MATERIALS AND METHODS

• Bayesian methodology was applied using historical data from FREEDOMS as the informative prior and appropriate prior distribution of model parameters, and the mean PBVC treatment difference between fingolimod 0.5 mg and placebo in FREEDOMS II was estimated.

• The methodology inferred the posterior probability as a consequence of two antecedents: a prior probability and a likelihood function derived from a statistical model of the observed data.

RESULTS

Study population

• Baseline demographics and disease characteristics were generally similar between studies and treatment groups, and were representative of an RRMS population with active disease.

Table 1. Patient baseline characteristics in FREEDOMS and FREEDOMS II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FREEDOMS (N=1277)</th>
<th>FREEDOMS II (N=1280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36.8 (9.77)</td>
<td>37.2 (9.80)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>296 (69.6)</td>
<td>298 (71.0)</td>
</tr>
<tr>
<td>Time since onset of first symptom, years</td>
<td>8.0 (6.60)</td>
<td>8.1 (6.35)</td>
</tr>
<tr>
<td>Number of relapses in the previous year</td>
<td>1.5 (1.07)</td>
<td>1.4 (1.07)</td>
</tr>
<tr>
<td>Number of relapses in the previous 2 years</td>
<td>2.1 (1.19)</td>
<td>2.2 (1.19)</td>
</tr>
<tr>
<td>EDDS score</td>
<td>2.3 (1.29)</td>
<td>2.5 (1.29)</td>
</tr>
<tr>
<td>Patients free from Gd+, gadolinium-enhancing lesions (%)</td>
<td>263 (65.2)</td>
<td>262 (65.0)</td>
</tr>
<tr>
<td>Number of Gd+ lesions</td>
<td>1.6 (1.57)</td>
<td>1.3 (1.29)</td>
</tr>
<tr>
<td>T2 lesion volume, mm3</td>
<td>6128 (7623)</td>
<td>6162 (7065)</td>
</tr>
<tr>
<td>Normalized BV, mL</td>
<td>1521 (83.16)</td>
<td>1512 (85.49)</td>
</tr>
</tbody>
</table>

PBVC in FREEDOMS and FREEDOMS II

• The original analysis of FREEDOMS data demonstrated a significant positive treatment difference (p<0.001) in PBVC at 24 months between patients treated with fingolimod 0.5 mg (mean [SD] PBVC, −0.84% [1.31]) and those who received placebo (mean [SD] PBVC, −1.31% [1.50]) (Figure 1A).

• The original analysis of FREEDOMS II data also demonstrated a significant positive treatment difference (p<0.001) in PBVC at 24 months between patients treated with fingolimod 0.5 mg (mean [SD] PBVC, −0.86% [1.22]) and those who received placebo (mean [SD] PBVC, −1.28% [1.50]) (Figure 1B).

Analysis of PBVC using Bayesian methodology

• The Bayesian analysis of FREEDOMS data with non-informative prior (zero weight given to FREEDOMS) produced a positive treatment difference in PBVC for patients treated with fingolimod relative to those who received placebo (mean [95% Bayesian credible interval (BCI)], 0.42% [0.19–0.67]) (Figure 2).

• Differences in PBVC between patients receiving fingolimod relative to those receiving placebo were assessed by two-sided ANCOVA with adjustment for study group, country and baseline BV at baseline.

• More sensitive estimates of the effect of fingolimod on PBVC may be obtained with Bayesian methodology, using prior evidence (FREEDOMS) to analyze FREEDOMS II data with probabilistic interpretation.

ACKNOWLEDGMENTS

Editorial support was provided by Oxford PharmaGenesis, Oxford, UK, which was funded by Novartis Pharmaceuticals Corporation. The final responsibility for the content lies with the authors.

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