Effect of oral fingolimod treatment on annualized relapse rates in patients with relapsing–remitting multiple sclerosis estimated using Bayesian methodology

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INTRODUCTION
• In the 2-year, randomized, double-blind phase 3 trials FREDOMS and FREDOMS II, fingolimod 0.5 mg was shown to have greater efficacy than placebo, as assessed by annualized relapse rates (ARRs) and magnetic resonance imaging outcomes, in the treatment of patients with relapsing-remitting multiple sclerosis (RRMS).1,2
• Estimates of ARRs (after adjusting for covariates) were made in the primary analyses using a negative binomial model (NBM), which is commonly used to summarize ARRs in clinical trials of MS therapies.3
• Bayesian methodology uses prior evidence for the analysis of current data.4,5 Power priors can incorporate historical data in a natural, systematic way. In the sensitivity analyses reported here, relapse data from FREDOMS were used as the informative prior with different weighting schemes in combination with current data from FREDOMS II to obtain the posterior estimates.

METHODS
Study designs and participants • FREDOMS and FREDOMS II included patients aged 18–55 years, with a diagnosis of RRMS defined using the 2005 revised McDonald criteria,5 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 enrolment.

Objectives • To estimate ARRs in patients with RRMS treated with fingolimod 0.5 mg once daily in the FREDOMS II study using Bayesian methodology.

METHODS
Study designs and participants • FREDOMS and FREDOMS II included patients aged 18–55 years, with a diagnosis of RRMS defined using the 2005 revised McDonald criteria,5 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 enrolment.

Methods • Bayesian power prior methodology used historical data from FREDOMS as the informative prior to estimate ARRs for fingolimod 0.5 mg versus placebo in FREDOMS II – 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.

CONCLUSIONS
• In the phase 3, placebo-controlled FREDOMS II trial of fingolimod in patients with RRMS, estimates of ARRs obtained using Bayesian power prior methodology were consistent with previously reported results that were calculated using a classic negative binomial model.
• Analysis of clinical datasets using prior clinical data and Bayesian methodology may improve estimates of treatment effects.

RESULTS
Study population (Table 1) • Baseline demographic and disease characteristics were mostly similar between studies and treatment groups, and were representative of an RRMS population with active disease.
• There were proportionately more women in FREDOMS than FREDOMS II, and on average, patients in FREDOMS II were older at baseline than those in FREDOMS and had a lower burden of disease even though a longer period had elapsed since they experienced the first symptoms of MS.

Analysis of ARR using the NBM • The analysis of FREDOMS II data using the NBM estimated a 47.8% reduction in ARR in patients treated with fingolimod (ARR, 0.21; 95% confidence interval [CI], 0.17–0.25) relative to placebo (ARR, 0.39; 95% CI, 0.34–0.46) (Figure 1).

Analysis of ARR using Bayesian methodology • The Bayesian analysis of FREDOMS II data with non-informative prior (zero weight given to FREDOMS study data) estimated a 48.2% reduction in ARR in patients treated with fingolimod (ARR, 0.20; 95% Bayesian credible interval [BCI], 0.17–0.25) relative to placebo (ARR, 0.39; 95% BCI, 0.33–0.47) (Figure 1).

Table 1. Patient baseline characteristics in FREDOMS and in FREDOMS II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FREDOMS (N=1272)</th>
<th>FREDOMS II (N=1083)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>36.5 (8.77)</td>
<td>37.2 (8.60)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>296 (69.6)</td>
<td>298 (71.3)</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 (0.76)</td>
<td>1.4 (0.73)</td>
</tr>
<tr>
<td>Number of relapses in the previous 2 years</td>
<td>2.1 (1.23)</td>
<td>2.1 (1.19)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>3.0 (2.9)</td>
<td>2.1 (2.1)</td>
</tr>
<tr>
<td>Patients free from Gd+ lesions, n (%)</td>
<td>263 (62.5)</td>
<td>262 (62.0)</td>
</tr>
<tr>
<td>Number of Gd+ lesions</td>
<td>1.6 (5.57)</td>
<td>1.3 (3.93)</td>
</tr>
<tr>
<td>T2 lesion volume (cm³)</td>
<td>6128 (7623)</td>
<td>6162 (7085)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) unless stated otherwise.

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing.

References

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