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

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CONCLUSIONS

- **In the phase 3, placebo-controlled FREEDOMS 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**

INTRODUCTION

- In the 2-year, randomized, double-blind phase 3 trials FREEDOMS and FREEDOMS 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[1,2]
- Bayesian methodology uses prior evidence for the analysis of current data.[3,4] Power priors can incorporate historical data in a natural, systematic way. In the sensitivity analyses reported here, relapse data from FREEDOMS were used as the informative prior with different weighting schemes in combination with current data from FREEDOMS II to obtain the posterior estimates
- Use of prior evidence from FREEDOMS may improve estimates of ARR based on current data from FREEDOMS II

OBJECTIVE

- To estimate ARRs in patients with RRMS treated with fingolimod 0.5 mg once daily in the FREEDOMS II study using Bayesian 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,[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
- Details of study designs and patient selection criteria have been previously published[1,2]
  - Confirmed relapses were defined in the study protocols as the appearance of a new neurological abnormality, or the worsening of a previously stable neurological abnormality, present for at least 24 hours in the absence of fever or infection and confirmed within 7 days of the onset of symptoms
  - Confirmation of relapse was made by an independent investigator and had to be accompanied by at least a 0.5-point increase on the EDSS, 1.0-point increases on two different functional systems of the EDSS or a 2.0-point increase on one functional system (excluding bowel/bladder or cerebral functional systems)

Analyses

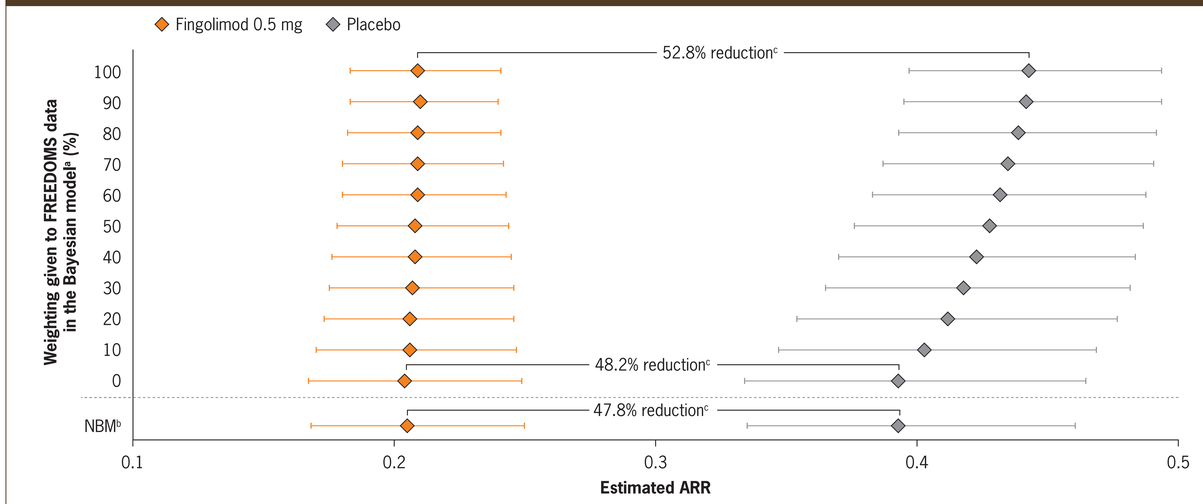
- In the primary analyses, between-treatment differences in ARR were estimated using the NBM, with treatment, country, number of relapses in the previous 2 years and baseline EDSS score as covariates
  - For the NBM, the response variable was the number of relapses for each patient, and a quadratic estimate of variance was used. The logarithm of time on study (in years) was the offset variable, which allowed hypothesis testing and estimation of relapse rates. The ARR and its confidence interval for each treatment group were estimated from the NBM
- Bayesian power prior methodology used historical data from FREEDOMS as the informative prior to estimate ARRs for fingolimod 0.5 mg versus placebo in FREEDOMS 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

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

Characteristic	FREEDOMS (N=1272)		FREEDOMS II (N=1083)	
	Fingolimod 0.5 mg (n=425)	Placebo (n=418)	Fingolimod 0.5 mg (n=358)	Placebo (n=355)
Age (years)	36.6 (8.77)	37.2 (8.60)	40.6 (8.39)	40.1 (8.42)
Women, n (%)	296 (69.6)	298 (71.3)	275 (76.8)	288 (81.1)
Time since onset of first symptom (years)	8.0 (6.60)	8.1 (6.35)	10.4 (8.01)	10.6 (7.85)
Number of relapses in the previous year	1.5 (0.76)	1.4 (0.73)	1.4 (0.86)	1.5 (0.93)
Number of relapses in the previous 2 years	2.1 (1.13)	2.2 (1.19)	2.2 (1.38)	2.2 (1.49)
EDSS score	2.3 (1.29)	2.5 (1.29)	2.4 (1.33)	2.4 (1.31)
Patients free from Gd+ lesions, n (%)	263 (62.0)	262 (63.0)	218 (61.1)	225 (63.6)
Number of Gd+ lesions	1.6 (5.57)	1.3 (2.93)	1.3 (3.37)	1.2 (3.23)
T2 lesion volume (mm^3)	6128 (7623)	6162 (7085)	5484 (8000)	5553 (7841)
Normalized brain volume (mL)	1521 (83.16)	1512 (85.49)	1522 (82.49)	1526 (85.19)

Data are mean (standard deviation) unless stated otherwise
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing

Figure 1. Mean estimated ARR (95% BCI) as a function of power prior weighting of FREEDOMS data in the Bayesian analysis of FREEDOMS II



[a]The weighting given to FREEDOMS data was increased in 10% increments from 0% to 100%, while the weighting given to FREEDOMS II data was fixed at 100%; therefore, 100% weighting of FREEDOMS data applied equal weight to both trials
[b]NBM values are mean estimated ARR and 95% confidence interval
[c]Reduction in ARR with fingolimod 0.5 mg relative to placebo
ARR, annualized relapse rate; BCI, Bayesian credible interval; NBM, negative binomial model

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 FREEDOMS II than FREEDOMS, and on average, patients in FREEDOMS II were older at baseline than those in FREEDOMS 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 FREEDOMS 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 FREEDOMS II data with non-informative prior (zero weight given to FREEDOMS 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**)
- Applying 100% weight to both the prior and current study data resulted in an estimated reduction in ARR of 52.8% in patients treated with fingolimod (ARR, 0.21; 95% BCI, 0.18–0.24) versus placebo (ARR, 0.44; 95% BCI, 0.40–0.49) (**Figure 1**)
- Power priors weighted from 0–100% were explored in increments of 10%

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Disclosures

Guosheng Yin has nothing to disclose. **Xiangyi Meng** and **Zahur Islam** are employees and stock holders of Novartis Pharmaceuticals Corporation.

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