Early Effect of Fingolimod on Clinical and MRI Outcomes in Relapsing Multiple Sclerosis

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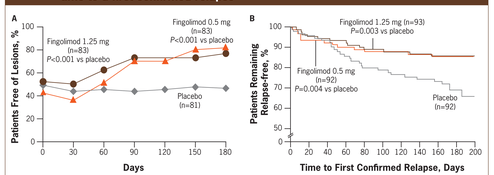
CONCLUSIONS

- **In FREEDOMS and FREEDOMS II, treatment with fingolimod 0.5 mg once daily significantly reduced the risk of relapse within 3 months and the development of new focal MRI lesions by the first postbaseline study scan at 6 months.**
- **Fingolimod reduced brain volume loss by approximately 35%–40% vs placebo over the first 6 months, a rate of reduction that was sustained through 2 years.**
- **The observed timing of early clinical efficacy appears consistent with results of a prior phase 2 study with monthly MRIs performed over 6 months.**
- **Effects on relapse, MRI lesions, and brain atrophy at 6 months appear consistent with 2-year outcomes, suggesting substantial early treatment benefits of fingolimod.**

INTRODUCTION

- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 other countries for treatment of relapsing multiple sclerosis (MS).[a]
- In a phase 2 study, fingolimod demonstrated significant improvement in magnetic resonance imaging (MRI) outcomes as early as month 2 and reduced the annualized relapse rate over 6 months **(Figure 1)**.[1]
- The expected time lag between start of treatment and onset of efficacy is an important consideration for MS therapy because early benefits may prevent excess morbidity.

Figure 1. Phase 2 study: (A) Proportions of patients free of gadolinium-enhancing lesions on T1-weighted MRI at 0–6 months and (B) Kaplan-Meier estimated time to a first confirmed relapse



MRI=magnetic resonance imaging.

OBJECTIVE

- To evaluate the early clinical and MRI effects of fingolimod at the approved 0.5-mg once-daily dose during the first 6 months of treatment in the Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS)[2] and FREEDOMS II[3] phase 3 studies

METHODS

- FREEDOMS and FREEDOMS II were 24-month, double-blind, randomized clinical trials comparing the efficacy and safety of oral fingolimod 0.5 or 1.25 mg once daily vs placebo in patients with relapsing forms of MS. Details of the trial designs and study methodologies have been presented elsewhere.[2,3] Brain MRI assessments were conducted at baseline and months 6, 12, and 24.
- Data from FREEDOMS and FREEDOMS II were analyzed for treatment differences between fingolimod 0.5 mg daily and placebo with regard to relapse and MRI endpoints within the first 6 months. Analyses were conducted on the intent-to-treat population without multiplicity adjustments.
- Prespecified efficacy outcomes up to or at 6 months included
  - Time to first confirmed relapse
  - Proportions of patients free of confirmed relapse
  - Proportions of patients free of T1 gadolinium (Gd)–enhancing lesions, new/newly enlarged T2 lesions, and both T1 Gd-enhancing and new/newly enlarged T2 lesions on brain MRI
  - Percentage brain volume loss
  - Mean numbers of T1 Gd-enhancing lesions and new/newly enlarging T2 lesions on brain MRI
- Post hoc exploratory analyses
  - Time at which the treatment effect on first confirmed relapse became significant: log-rank test
  - Kaplan-Meier estimates of the proportions of patients free of confirmed relapse at 3 and 6 months: reduction vs placebo was calculated based on (1 – hazard ratio), where hazard ratio is derived from Cox proportional hazards model adjusted for treatment, country (FREEDOMS) or region (FREEDOMS II), baseline number of relapses in previous 2 years, and baseline Expanded Disability Status Scale score.
- Disability progression was not evaluated in this analysis of early treatment effects because assessment of confirmed disability progression over a short time frame (6 months) is not meaningful.

RESULTS

Early Treatment Effects on Relapse

- Treatment effects in delaying time to first confirmed MS relapse ($P<0.05$) were observed as early as day 82 in FREEDOMS and day 64 in FREEDOMS II **(Figure 2)**.
- Kaplan-Meier estimates showed that a significantly higher percentage of patients treated with fingolimod 0.5 mg once daily compared with placebo were free of confirmed relapse at 3 and 6 months **(Table 1)**.
  - In FREEDOMS, Kaplan-Meier estimates for fingolimod 0.5 mg vs placebo were 91.5% vs 86.5% at 3 months ($P=0.025$) and 86.5% vs 77.9% at 6 months ($P<0.001$).
  - In FREEDOMS II, Kaplan-Meier estimates for fingolimod 0.5 mg vs placebo were 92.9% vs 87.8% at 3 months ($P=0.035$) and 87.4% vs 77.9% at 6 months ($P<0.001$).

Figure 2. Time to first confirmed relapse in (A) FREEDOMS and (B) FREEDOMS II

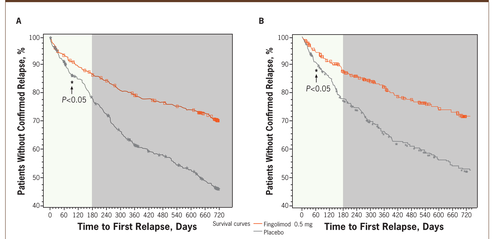


Table 1. Kaplan-Meier estimates of the percentage of patients free of confirmed relapse at 3 and 6 months

	Patients free of confirmed relapse, %					
	3 Months			6 Months		
	Fingolimod 0.5 mg	Placebo	*P* value*	Fingolimod 0.5 mg	Placebo	*P* value*
FREEDOMS	91.5	86.5	0.025	86.5	77.9	<0.001
FREEDOMS II	92.9	87.8	0.035	87.4	77.9	<0.001

**P values for treatment comparison are based on log-rank test using days 104 and 194 as cutoffs for censuring at months 3 and 6, respectively.*

Early Treatment Effects on MRI Lesions

- In FREEDOMS and FREEDOMS II at 6 months, a significantly higher percentage of patients in the fingolimod 0.5-mg group were free of MRI lesion activity compared with patients in the placebo group, including Gd-enhancing T1 lesions, new/newly enlarged T2 lesions, and both Gd-enhancing T1 lesions and new/newly enlarged T2 lesions **(Table 2)**.

Table 2. Percentage of patients free of new inflammatory MRI focal lesion activity at 6 months

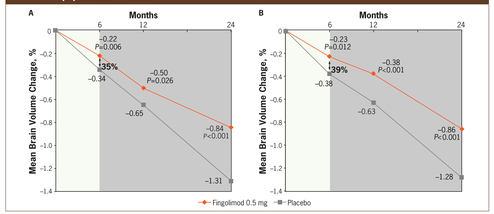
	Patients free of new inflammatory MRI activity, %					
	FREEDOMS			FREEDOMS II		
	Fingolimod 0.5 mg	Placebo	*P* value	Fingolimod 0.5 mg	Placebo	*P* value
Gd-enhancing T1 lesions	89.6	62.2	<0.001	87.6	63.4	<0.001
New/newly enlarged T2 lesions	64.7	38.1	<0.001	66.7	42.5	<0.001
Gd-enhancing T1 lesions and new/newly enlarged T2 lesions	65.0	39.4	<0.001	66.4	42.3	<0.001

Gd=gadolinium; MRI=magnetic resonance imaging.

Early Treatment Effects on Brain Atrophy

- Significant differences in the reduction in brain volume loss were seen at 6 months in FREEDOMS **(Figure 3A)** and FREEDOMS II **(Figure 3B)**. The differences from placebo were sustained over 2 years in both trials.

Figure 3. Percentage brain volume change (months 0–6) in (A) FREEDOMS and (B) FREEDOMS II



Summary of 6-Month and 24-Month Outcomes

- At 6 months, differences favoring fingolimod over placebo were observed in the estimated percentage of patients free of confirmed relapse, mean number of T1 Gd-enhancing lesions and new/newly enlarged T2 lesions, as well as brain volume loss **(Table 3)**.
- The observed differences vs placebo at 6 months were sustained over 2 years in both trials.

Table 3. Summary of treatment outcomes in FREEDOMS and FREEDOMS II

		6 Months			24 Months		
Outcome	Trial	Fingolimod 0.5 mg	Placebo	Reduction vs placebo, %	Fingolimod 0.5 mg	Placebo	Reduction vs placebo, %
Patients free of relapse, %*	FREEDOMS	86.5	77.9	39	70.4	45.6	52
	FREEDOMS II	87.4	77.9	46	71.5	52.7	48
Gd-enhancing T1 lesions, n†	FREEDOMS	0.2	1.3	85	0.2	1.1	82
	FREEDOMS II	0.2	1.1	82	0.4	1.2	67
New/newly enlarged T2 lesions, n†	FREEDOMS	1.0	3.6	72	2.5	9.8	74
	FREEDOMS II	0.8	2.9	72	2.3	8.9	74
Brain volume, % change from baseline†	FREEDOMS	−0.22	−0.34	35	−0.84	−1.31	36
	FREEDOMS II	−0.23	−0.38	39	−0.86	−1.28	33

Gd=gadolinium.
**Kaplan-Meier estimates. †Mean values shown.*

References

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2. Kappos L, et al. *N Engl J Med.* 2010;362(5):387-401.
3. Calabresi PA. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS): Results from an additional 24-month double-blind, placebo-controlled study (FREEDOMS II Study). Presented at: American Academy of Neurology 64th Annual Meeting; April 25, 2012; New Orleans, LA.

Disclosures

P. S. Chin, X. Meng, and R. Hashmonay are employees and stockholders of Novartis Pharmaceuticals Corporation.

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[a]The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.