Fingolimod Efficacy and Safety vs Placebo: Phase 3 FREEDOMS II Study

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CONCLUSIONS

- **These results from the FREEDOMS II study confirm data from the earlier FREEDOMS I and TRANSFORMS studies and demonstrate the clinical benefits and MRI outcomes seen in previous phase 3 studies.**
  - **Treatment with fingolimod significantly reduced ARR compared with placebo, regardless of baseline demographics, disease severity, or prior treatment with disease-modifying agents.**
  - **Significantly less brain atrophy was seen with fingolimod compared with placebo, with the difference observed as early as 6 months and sustained throughout the 24-month study.**
- **Safety and tolerability were consistent with the well-characterized safety profile of fingolimod.**

BACKGROUND

- 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 the largest clinical development program in relapsing MS, fingolimod has consistently demonstrated superior efficacy over the approved first-line treatment, interferon (IFN) β-1a intramuscular (Avonex®),[1] and placebo[2,3] in clinical and magnetic resonance imaging (MRI) outcome measures, including brain atrophy.
- This additional phase 3 FREEDOMS II trial was undertaken to evaluate the efficacy, safety, and tolerability of fingolimod vs placebo for up to 24 months in patients with relapsing-remitting MS (RRMS).

OBJECTIVE

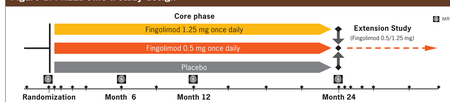
- To report the efficacy, safety, and tolerability of fingolimod compared with placebo and to evaluate responses in predefined patient subgroups in the FREEDOMS II study

METHODS

Study Design

- FREEDOMS II was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of once-daily fingolimod (0.5 mg or 1.25 mg) vs placebo **(Figure 1)**.

Figure 1. FREEDOMS II study design



MRI=magnetic resonance imaging.

- Primary objective: to demonstrate that fingolimod 0.5 mg was superior to placebo in reducing the annualized relapse rate (ARR), defined as the number of confirmed relapses per year.
- Secondary efficacy endpoints
  - Brain atrophy (percentage change from baseline in brain volume), measured by structural image evaluation using normalization of atrophy
  - Time to 3-month confirmed disability progression, assessed using the Expanded Disability Status Scale (EDSS) score (1-point EDSS change; 0.5-point if baseline EDSS was >5.0)
  - Time to first relapse and proportion of relapse-free patients
  - Safety endpoints: adverse events (AEs) of special interest

Key Assessments

- ARR was evaluated in subgroups defined by
  - Baseline demographics: sex, age, treatment history
  - Baseline disease activity: presence or absence of gadolinium (Gd)–enhancing T1 lesions, number of relapses in the 1 or 2 years before study start (0, 1, and ≥2 or 1, 2–3, and >5, respectively), and presence/absence of high disease activity (≥1 Gd-enhancing lesion and ≥2 relapses in the year before the study)
  - Baseline disease severity as determined by T2 lesion volume (≤3300 mm^3, less severe; >3300 mm^3, more severe) and EDSS score (<3, mild disability; ≥3, moderate–severe disability)
- Treatment comparisons between fingolimod 0.5 mg and placebo were performed using the negative binomial regression model adjusted for treatment, region, number of relapses in previous 2 years, and baseline EDSS. For 3 subgroups in which the model fitting did not converge, a simple model adjusted for treatment only was used (patients with: ≥3 Gd-enhancing T1 lesions; no relapses in the previous year; and >5 relapses in previous 2 years). Data are expressed graphically in Forest plots as ARR ratios for fingolimod 0.5 mg vs placebo with 95% CI.

[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.*

RESULTS

Patients

- Baseline patient demographics, disease characteristics, and MRI features were balanced across randomized study groups and were representative of the general RRMS population **(Table 1)**.

Table 1. Baseline demographics and disease characteristics of randomized patients*

	Placebo (n=355)	Fingolimod 0.5 mg (n=358)	Fingolimod 1.25 mg (n=370)
Patient demographics			
Age, y	40.1 (8.4)	40.6 (8.4)	40.9 (8.9)
Women, n (%)	288 (81)	275 (77)	281 (76)
White, n (%)	310 (87)	319 (89)	333 (90)
Prior use of DMT, n (%)	259 (73)	264 (74)	287 (78)
Disease characteristics			
Time since first MS symptom, y	10.6 (7.9)	10.4 (8.0)	10.8 (8.2)
Number of relapses in past 1 y	1.5 (0.9)	1.4 (0.9)	1.5 (1.0)
Number of relapses in past 2 y	2.2 (1.5)	2.2 (1.4)	2.3 (2.0)
EDSS score, mean (SD)/median	2.4 (1.3)/2.0	2.4 (1.3)/2.0	2.4 (1.3)/2.5
MSFC z-score, median	0.13	0.18	0.11
MRI features			
Gd-enhancing T1 lesion count	1.2 (3.2)	1.3 (3.4)	1.3 (3.6)
Proportion free of Gd-enhancing T1 lesions, n/N (%)	225/354 (64)	218/358 (61)	254/367 (69)

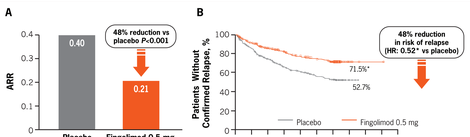
DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd=gadolinium; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSFC=Multiple Sclerosis Functional Composite.
**All data are mean (SD) unless otherwise noted.*

- Nearly all patients (95%) were from the United States, and 75% had previously been treated with disease-modifying therapies. The most commonly used prior treatment was IFNβ (62%).
- Of the 1083 patients randomly assigned to treatment, 778 (72%) completed the study.
  - Study completion rates were similar between treatment groups: fingolimod 0.5 mg, 272 patients (76%); fingolimod 1.25 mg, 251 patients (68%); placebo, 255 patients (72%).

Efficacy

- Fingolimod significantly reduced ARR over 24 months compared with placebo. At the approved 0.5-mg dose, fingolimod reduced ARR by 48% vs placebo (ARR ratio = 0.516; $P<0.001$; **Figure 2A**); a 50% reduction was observed with fingolimod 1.25 mg (ARR ratio = 0.503; $P<0.001$ vs placebo).
  - The proportion of patients free from MS relapse at month 24 was also increased with fingolimod 0.5 mg vs placebo (71.5% vs 52.7%; **Figure 2B**).
- ARR was significantly reduced by fingolimod 0.5 mg compared with placebo across subgroups defined by baseline demographics (**Figure 3A**), regardless of baseline disease activity (**Figure 3B**), and irrespective of baseline disease severity (**Figure 3C**).
- The decrease in brain volume was significantly less with fingolimod than with placebo (fingolimod 0.5 mg: 33% reduction vs placebo at month 24, $P<0.001$, **Figure 4**; fingolimod 1.25 mg: 53% reduction vs placebo, $P<0.001$).
- Patients receiving fingolimod also showed a numerically reduced risk of 3-month confirmed disability progression at the approved dose of 0.5 mg compared with patients receiving placebo (fingolimod 0.5 mg: 17% reduction vs placebo, $P=0.227$; **Figure 5**); a 28% reduction was seen with fingolimod 1.25 mg ($P=0.041$).

Figure 2. (A) Aggregate ARR up to month 24 by treatment and (B) proportions of relapse-free patients and time to first relapse by treatment

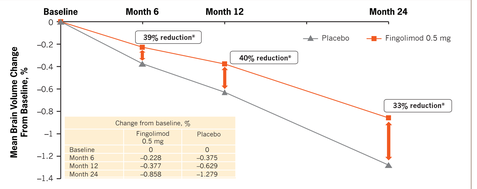


Aggregate ARR estimate and P value are calculated using negative binomial regression adjusted by treatment, region, number of relapses in the previous 2 years, and baseline EDSS.

Log-rank test was used to compare the survival distribution between treatment groups. HR from Cox proportional hazard model adjusted for treatment, region, baseline EDSS, and number of relapses in previous 2 years.
**Indicates 2-sided statistical significance at 0.05 level*

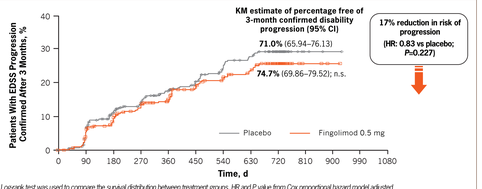
ARR=annualized relapse rate; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

Figure 4. Percentage brain volume change from baseline to month 24 by treatment



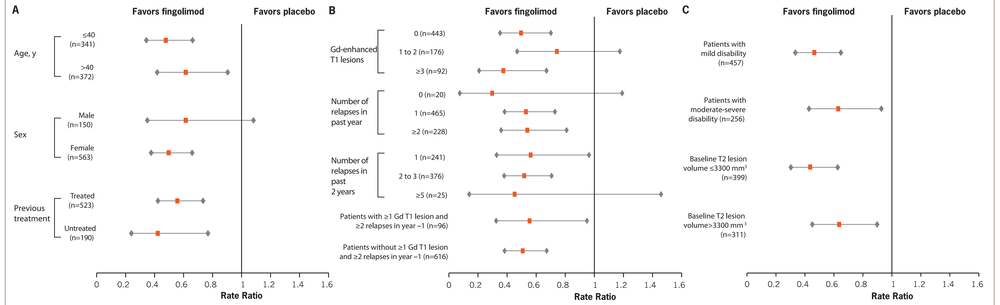
Descriptive statistics used for percentage change from baseline, P values are from rank analysis of covariance adjusted for treatment, regions, and baseline normalized brain volume.
**Indicates 2-sided statistical significance at 0.05 level.*

Figure 5. Time to 3-month confirmed disability progression



Log-rank test was used to compare the survival distribution between treatment groups. HR and P value from Cox proportional hazard model adjusted for treatment, region, baseline EDSS, and age.
EDSS=Expanded Disability Status Scale; HR=hazard ratio; KM=Kaplan-Meier; n.s.=not significant.

Figure 3. ARR ratios at month 24 for all study subgroups based on (A) patient demographics, (B) baseline disease activity, and (C) baseline disease severity



ARR=annualized relapse rate; Gd=gadolinium.
Data are expressed as ARR ratios for fingolimod vs placebo with 95% CI

Safety

- AEs of special interest occurring more frequently with fingolimod than with placebo are shown in **Table 2**.
- No deaths occurred with fingolimod treatment.
- Asymptomatic, dose-dependent elevations of liver enzymes were observed in patients receiving fingolimod. Liver enzyme levels improved following discontinuation of therapy, and no patient developed liver failure. No cases met criteria for Hy's law indication of drug-induced liver injury.

Table 2. Adverse events of special interest

AE, n (%)	Placebo (n=355)	Fingolimod 0.5 mg (n=358)	Fingolimod 1.25 mg (n=370)
First-dose cardiac events	43 (12.1)	43 (12.0)	44 (11.9)
Symptomatic bradycardia	1 (0.3)	3 (0.8)	15 (4.1)
Mobitz I (Wenckebach) AV block	7 (2.0)	12 (3.4)	24 (6.7)
2:1 AV block	0 (0.0)	6 (1.7)	12 (3.3)
Hypertension*†	11 (3.1)	32 (8.9)	47 (12.7)
Infections	255 (71.8)	263 (73.5)	269 (72.7)
Herpes viral‡‖	19 (5.4)	30 (8.4)	35 (9.5)
Herpes zoster	3 (0.8)	9 (2.5)	12 (3.2)
Influenza	24 (6.8)	34 (9.5)	26 (7.0)
Lymphopenia†	0 (0.0)	27 (7.5)	36 (9.7)
Leukopenia	0 (0.0)	3 (0.8)	4 (1.1)
Macular edema	2 (0.6)	3 (0.8)	4 (1.1)
Basal-cell carcinoma‡‖	2 (0.6)	10 (2.8)	6 (1.6)
Abnormal LFT†			
≥3-fold ALT increase	8 (2.3)	25 (7.0)	35 (9.6)
≥5-fold ALT increase	4 (1.1)	8 (2.2)	7 (1.9)

AE=adverse event; ALT=alanine aminotransferase; AV=atrioventricular; LFT=liver function test.
**Higher incidence of hypertension as an AE in both active treatment groups compared with previous pivotal studies.*
†*AEs of interest reported more frequently with fingolimod than placebo.*
‡*An integrated analysis of 3 pivotal phase 3 studies and a phase 2 study did not confirm this finding.*

References

1. Cohen JA, et al. *N Engl J Med.* 2010;362:402-415.
2. Kappos L, et al. *N Engl J Med.* 2006;355:1124-1140.
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Disclosures

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