# Key results from PREFER*MS*: real-world patient retention and outcomes on fingolimod versus platform injectable disease-modifying therapies in early relapsing–remitting MS

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## CONCLUSIONS

- **Fingolimod is associated with higher therapeutic retention, improved clinical and MRI outcomes, and greater treatment satisfaction than iDMTs in patients with early RRMS**

## BACKGROUND

- Multiple sclerosis (MS) is a chronic, demyelinating, immune-mediated disease of the central nervous system[1,2]
- Injectable disease-modifying therapies (iDMTs) are typically used first-line, but suboptimal adherence to iDMT classes is common[3,4]
- High-efficacy drugs such as fingolimod are often used as second-line therapy; fingolimod 0.5 mg is approved as a first-line therapy, and can be used early in the disease course[5]
- PREFER*MS* (Prospective, Randomized, active-controlled, open-label study to Evaluate patient retention of Fingolimod vs approved first-line disease-modifying therapies in adults with Relapsing–remitting Multiple Sclerosis) was the first large randomized study of treatment retention comparing fingolimod with iDMTs over 12 months

## OBJECTIVE

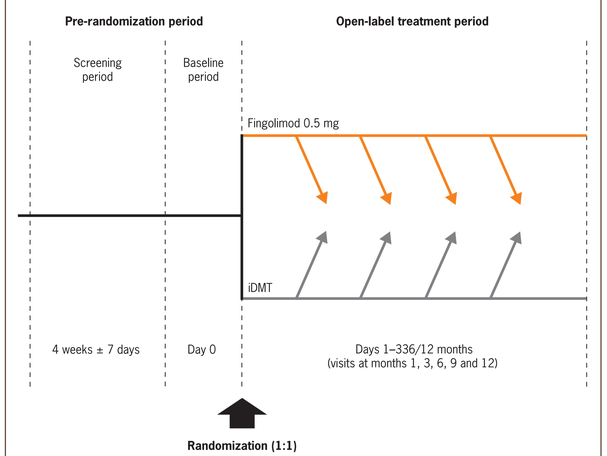
- To examine therapeutic retention with fingolimod 0.5 mg versus iDMTs in PREFER*MS*

## METHODS

### *Study design*

- 12-month, phase 4, open-label, active-controlled, randomized, multicenter study conducted at 117 sites in the USA
- Enrolled patients with RRMS[6] were treatment-naïve or had received only one iDMT class (interferon β or glatiramer acetate)

**Figure 1. PREFER*MS* study design**




Patients were allowed one switch from randomized treatment
Reason for switch <3 months: safety or efficacy
Reason for switch at 3–12 months: safety, efficacy, tolerability or convenience

- Patients randomized (1:1) to fingolimod 0.5 mg or to a pre-selected iDMT were followed up quarterly for 12 months (**Figure 1**)
- A single on-study treatment switch was allowed after a minimum of 3 months of treatment, unless related to efficacy or safety; switches due to efficacy or safety were allowed at any month following randomization (**Figure 1**)

### *Analyses*

- Primary endpoint: percentage of patients retained on randomized treatment for 12 months
- Secondary endpoints included clinical assessments, magnetic resonance imaging (MRI), safety assessments and patient-reported outcomes[7,8]
- Sample size and power calculations were based on retention rates
- No adjustments were made for multiple comparisons
- To adjust for differences in treatment exposure, rates of adverse events were calculated per patient-year, determined as the sum of the number of days on study drug for all patients in the group divided by 365.25
- Statistical tests are described in the footnotes that accompany the tables and figures

## RESULTS

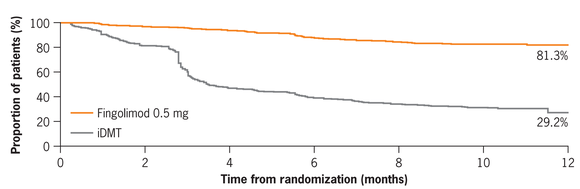
**Table 1. Summary of patient demographic and baseline characteristics**

| Demographic and baseline characteristics[a] | Fingolimod 0.5 mg (n=436) | iDMT (n=439) | p-value |
|---|---|---|---|
| Age, years | 41.5 (10.84) | 41.9 (10.39) | 0.6310 |
| Sex, n (%)<br>Male<br>Female | <br>125 (28.7)<br>311 (71.3) | <br>110 (25.1)<br>329 (74.9) | 0.2282 |
| Race, n (%)<br>Caucasian<br>Black<br>Asian<br>Native American<br>Pacific Islander<br>Other | <br>355 (81.4)<br>69 (15.8)<br>1 (0.2)<br>1 (0.2)<br>0<br>10 (2.3) | <br>355 (80.9)<br>72 (16.4)<br>1 (0.2)<br>1 (0.2)<br>2 (0.5)<br>8 (1.8) | 0.6553 |
| Height, cm | 168.5 (8.99) | 167.5 (10.06) | 0.1388 |
| Weight, kg | 82.94 (20.1) | 83.56 (22.3) | 0.6651 |
| BMI, kg/m$^2$ | 29.19 (6.70) | 29.76 (7.55) | 0.2335 |
| Duration of MS since diagnosis, years | n=434<br>4.42 (6.67) | n=434<br>4.21 (5.94) | 0.6314 |
| Duration of MS since first symptoms, years | n=434<br>7.29 (8.21) | n=434<br>7.21 (7.66) | 0.8871 |
| Number of relapses in the past year | n=430<br>0.6 (0.95) | n=436<br>0.6 (0.94) | 0.6041 |
| Number of relapses in the past 2 years | n=430<br>0.9 (1.51) | n=436<br>0.9 (1.41) | 0.6752 |
| EDSS score | n=433<br>2.36 (1.56) | n=427<br>2.44 (1.51) | – |
| T2 lesion volume, cm$^3$ | n=431<br>7.65 (11.60) | n=415<br>7.44 (10.17) | – |
| Normalized brain volume, cm$^3$ | n=431<br>1521.42 (83.9) | n=412<br>1511.19 (90.5) | – |
| Number of Gd+ lesions | n=429<br>1.08 (3.75) | n=414<br>0.85 (3.03) | – |

[a]Data shown are mean (SD) unless stated otherwise
Treatment group comparisons were made using the Cochran–Mantel–Haenszel test for categorical variables and a two-sample *t*-test for continuous variables
BMI, body mass index

- 875 patients with RRMS were randomized (fingolimod, n=436; iDMT, n=439). At baseline, mean time since diagnosis was 4.3 years (considered an early RRMS population) and the mean Expanded Disability Status Scale (EDSS) score was 2.4. Patient demographic and baseline characteristics were similar between treatment groups (**Table 1**)

**Figure 2. Retention rates in PREFER*MS* during the open-label randomized treatment period, tested for significance using four statistical methods**

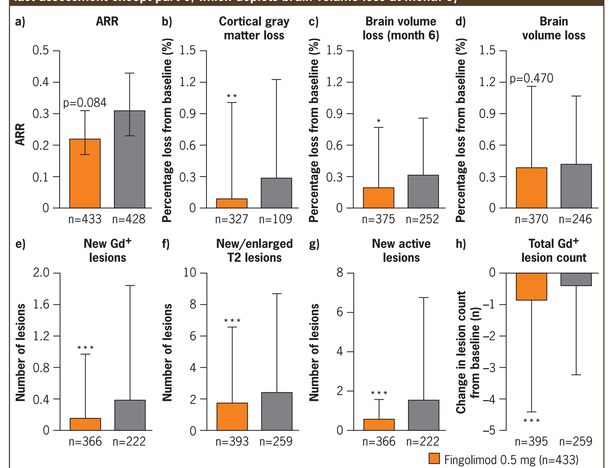



| | Fingolimod 0.5 mg (n=433) | iDMT (n=428) | Total (N=861) |
|---|---|---|---|
| Completed study on randomized treatment, n (%) | 352 (81.3) | 125 (29.2) | 477 (55.4) |
| **Statistical method** | **Test** | **Statistic** | **p-value** |
| Cochran–Mantel–Haenszel | $\chi^2$ | 234.5138 | <0.0001 |
| Logistic regression | Odds ratio | 10.5095 | <0.0001 |
| Cox proportional hazard | Hazard ratio | 0.1595 | <0.0001 |
| Kaplan–Meier | Log-rank | NA | <0.0001 |
| Normal approximation | Difference (95% CI) | 0.5209 (0.46, 0.58) | |

Cochran–Mantel–Haenszel, logistic regression and the Cox proportional hazard models are adjusted for treatment and treatment naivety. Kaplan–Meier log-rank test is adjusted for treatment, and normal approximation is performed using continuity correction. Note: for all percentages, the denominator is the total number of patients (n) in the treatment group

- Of the 861 patients (98.4%) who completed the study (full analysis set), 477 (55.4%) completed the study while still receiving the randomized treatment (**Figure 2**)
- Patient retention was significantly higher with fingolimod than with iDMT (352 [81.3%] vs 125 [29.2%]; p<0.0001) (**Figure 2**)

**Figure 3. Clinical and MRI outcomes from the PREFER*MS* study (all graphs show data obtained at last assessment except part c, which depicts brain volume loss at month 6)**

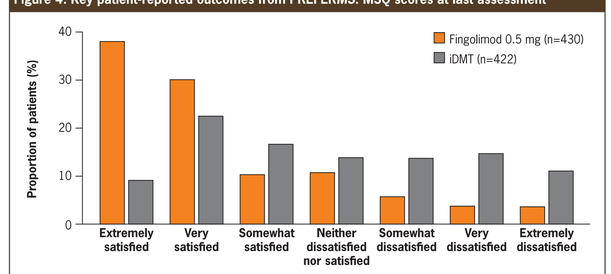



*p<0.05; **p<0.01; ***p<0.0001 versus iDMT
Bars indicate SD except in panel a, in which they represent 95% confidence intervals
Panel a: negative binomial regression adjusted for treatment, number of relapses in the previous 2 years, screening EDSS score and treatment naivety, using duration (years) as an offset variable
Panels b–d: rank analysis of covariance adjusted for treatment, treatment naivety, corresponding baseline values and age
Panels e–h: negative binomial regression adjusted for treatment, number of relapses in previous 2 years, screening EDSS score and treatment naivety, using duration (years) as an offset variable

### *Clinical and MRI outcomes*

- There was a statistical trend for a lower annualized relapse rate in patients treated with fingolimod than in those treated with iDMT (ratio, 0.70; p=0.084), despite shorter iDMT exposure (**Figure 3a**)
- Compared with MRI outcomes in the iDMT group, at last assessment (randomized phase) (**Figure 3b–h**), patients treated with fingolimod had:
  - less cortical gray matter loss (p<0.01)
  - less brain volume loss at month 6 (p<0.05; no significant difference at last assessment: p=0.4705)
  - fewer new gadolinium-enhancing (Gd+) lesions (p<0.0001)
  - fewer new/enlarged T2 lesions (p<0.0001)
  - fewer new active lesions (p<0.0001)
  - greater mean reduction from baseline in total Gd+ lesion count (p<0.0001)

**Figure 4. Key patient-reported outcomes from PREFER*MS*: MSQ scores at last assessment**




Cochran–Mantel–Haenszel test using modified ridit scores adjusted for treatment and treatment naivety. Overall difference across categories between fingolimod 0.5 mg and iDMTs is significant, p<0.0001

### *Patient-reported outcomes*

- Treatment satisfaction (as measured by the Medication Satisfaction Questionnaire [MSQ]) was greater in the fingolimod group than in the iDMT group (p<0.0001 at last assessment) (**Figure 4**)

**Table 2. Summary of AEs during the randomized open-label treatment phase of PREFER*MS* (safety population)**

| Preferred term | Rate (AE/patient-year) | |
|---|---|---|
| | Fingolimod 0.5 mg (n=433) | iDMT (n=428) |
| **Any AE** | **4.008** | **7.011** |
| **AEs leading to treatment discontinuation, total** | **0.112** | **0.540** |
| General disorders and administration site conditions | 0.011 | 0.420 |
| Injection-site reaction | 0.000 | 0.131 |
| Influenza-like illness | 0.003 | 0.096 |
| Injection-site pain | 0.000 | 0.091 |
| Fatigue | 0.000 | 0.045 |
| Injection-site erythema | 0.000 | 0.035 |
| Injection-site pruritus | 0.000 | 0.035 |
| Musculoskeletal and connective tissue disorders | 0.006 | 0.040 |
| Myalgia | 0.003 | 0.030 |
| Nervous system disorders | 0.017 | 0.055 |
| Headache | 0.006 | 0.040 |
| Psychiatric disorders | 0.000 | 0.075 |
| Anxiety | 0.000 | 0.045 |
| **Serious AEs** | **0.083** | **0.076** |
| Infections and infestations | 0.019 | 0.000 |
| Pneumonia | 0.006 | 0.000 |
| Metabolism and nutrition disorders | 0.006 | 0.000 |
| Dehydration | 0.006 | 0.000 |
| Nervous system disorders | 0.022 | 0.040 |
| MS relapse | 0.014 | 0.025 |
| Psychiatric disorders | 0.011 | 0.010 |
| Anxiety | 0.003 | 0.010 |
| Suicidal ideation | 0.006 | 0.000 |

AEs causing study drug discontinuation are reported for events affecting at least 1% of patients in either treatment group. Rates of serious AEs are reported for events affecting at least two patients in either treatment group

### *Safety assessments*

- Most adverse events (AEs) were mild or moderate in severity
- AEs per patient-year and AEs per patient-year leading to treatment discontinuation were higher with iDMTs than with fingolimod (**Table 2**)
- Higher rates of treatment discontinuation in the iDMT group were mainly attributable to higher rates of injection-site conditions, fatigue and influenza-like symptoms (**Table 2**)
- Serious AEs per patient-year were similar in the two treatment groups (**Table 2**)
- Safety outcomes for all treatments were consistent with the respective US prescribing information

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