Subgroup and sensitivity analyses of treatment retention in patients participating in the PREFERMS Study

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Introduction

- Among patients with multiple sclerosis (MS), suboptimal adherence to injectable disease-modifying therapies (iDMTs) is common and reduces therapeutic effectiveness.^{1,2}
- PREFERMS was the first large, randomized, prospective study comparing treatment retention in patients with relapsing forms of MS treated with fingolimod 0.5 mg/day or an iDMT.³
- In PREFERMS, treatment retention with fingolimod was significantly greater than with iDMTs.³

Objective

Determine whether the greater rate of treatment retention seen with fingolimod than with iDMTs in the full analysis set (FAS) of PREFERMS was robust to sensitivity and subgroup analyses.

Methods

Study design

- Primary endpoint: patient retention on randomized treatment over 12 months. Enrolled patients with relapsing forms of MS were treatment naïve or had received no more than one class of iDMT (interferon β or glatiramer acetate). Patients were randomized (1:1) to fingolimod or pre-selected iDMT and
- followed up quarterly for 12 months.
- A single on-study treatment switch was allowed after 3 months, or earlier for efficacy or safety reasons (**Figure 1**).

Analyses

- Retention analyses: conducted during the open-label randomized treatment period.
- Sensitivity analysis: conducted in the FAS, excluded patients who switched treatment neither for safety nor efficacy reasons before day 84 (when switching for convenience became permissible), and patients who switched treatment between days 77 and 110.
- Subgroup analyses: conducted in the FAS.
- Between-group differences in retention calculated by normal approximation using continuity correction.
- Significance estimated using the Cochran–Mantel–Haenszel test, adjusted for treatment and treatment naïvety.
- The study was not powered for subgroup analyses.

Results

- 875 patients randomized; patient demographics and baseline characteristics were similar in the two treatment groups (Table 1).
- 861 patients included in the FAS.³
- Retention rate on randomized treatment in the FAS was significantly greater with fingolimod than iDMTs (**Figure 2a**). Mean duration of exposure to fingolimod was nearly twice that of iDMTs (301 vs 163 days).

Figure 1. PREFERMS study design

	Pre-	random
		Screenin period
		4 weeks £ 7 days
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PREFERMS was a 12-month, phase 4, open-label, active-controlled, randomized, multicenter study (117 sites) in the United States.



Table 1. PREFERMS patient demographics and baseline characteristics

Demographics and baseline	Fingolimod	iDMT	p-value	
characteristics*	(n=436)	(n=439)		
Age, years	41.5 (10.84)	41.9 (10.39)	0.6310	
Sex, n (%)				
Male	125 (28.7)	110 (25.1)	0.2282	
Female	311 (71.3)	329 (74.9)		
Race, n (%)				
Caucasian	355 (81.4)	355 (80.9)		
African American	69 (15.8)	72 (16.4)		
Asian	1 (0.2)	1 (0.2)	0.6553	
Native American	1 (0.2)	1 (0.2)		
Pacific Islander	0	2 (0.5)		
Other	10 (2.3)	8 (1.8)		
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/m²	29.19 (6.70)	29.76 (7.55)	0.2335	
Duration of MS since diagnosis,	n=434	n=434	0.6314	
years	4.42 (6.67)	4.21 (5.94)		
Duration of MS since first	n=434	n=434	0 0071	
symptoms, years	7.29 (8.21)	7.21 (7.66)	0.0071	
Number of releases in the post wear	n=430	n=436	0.6041	
Number of relapses in the past year	0.6 (0.95)	0.6 (0.94)		
Number of relapses in the	n=430	n=436	0 6750	
past 2 years	0.9 (1.51)	0.9 (1.41)	0.0752	
	n=433	n=427		
ED33 Score	2.36 (1.56)	2.44 (1.51)		
T2 locion volume em ³	n=431	n=415		
rz iesion volume, cm [°]	7.65 (11.60)	7.44 (10.17)		
Normalized brain values and	n=431	n=412		
inormalized prain volume, cm [°]	1521.42 (83.9)	1511.19 (90.5)		
Number of gadolinium-enhancing	n=429	n=414		
lesions	1.08 (3.75)	0.85 (3.03)	—	

^aData shown are mean (SD) unless stated otherwis 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; EDSS, Expanded Disability Status Scale.

Sensitivity analyses

- Retention rate in the iDMT group decreased from month 3 to month 4 (days 77-110; **Figure 2a**).
- 126 patients switched from an iDMT to fingolimod.
- Most common reasons patients cited for switching included flu-like symptoms (n=22), injection-site reaction (n=22) and inconvenient administration (n=21) (**Table 2**).

Table 2. Primary reasons for discontinuing randomized treatment between days 77 and 110

Reason	Randomized treatment		
	iDMT (n=126)	Fingolimod 0.5 mg (n=4)	
Flu-like symptoms	22 (17.5)		
Injection-site reaction	22 (17.5)		
Inconvenient administration	21 (16.7)		
Frequency of injection	20 (15.9)		
Needle phobia	9 (7.1)		
Occurrence of relapse	3 (2.4)	1 (25.0)	
MRI disease activity	2 (1.6)		
Depression	2 (1.6)		
Hepatic side effects	1 (0.8)	3 (75.0)	
Lipoatrophy	1 (0.8)	_	
Spasticity	1 (0.8)	_	
Other ^a	22 (17.5)		

Data are n (%).

^aIncluded the following reasons: patient opted to switch treatment, n=9; injection-site pain, sensitivity or intolerance, n=5; dissatisfaction with treatment, convenience or dislike of injections, n=4; generalized aching, feeling unwell, n=3; efficacy, n=1.

MRI, magnetic resonance imaging.

reasons unrelated to efficacy or safety^a



Figure 3. Retention rates on fingolimod and iDMTs in the FAS and by subgroup

Parameter	Fingolin % retai
FAS	81.3 (
Subgroup	
Treatment naïve at enrollment	78.7 (
Previously treated	83.8 (
Age ≤40 years	83.1 (
Age >40 years	79.6 (
0-2 relapses in the 2 years before enrollment	83.0 (
≥3 relapses in the 2 years before enrollment	68.4
Baseline EDSS score 0.0-3.5	83.9 (
Baseline EDSS score ≥4.0	69.6
Women	80.2 (
Men	84.0 (
African American	80.6
Caucasian	80.8 (
Hispanic	91.7
Employed ^a	83.2 (
Unemployed ^b	77.9 (

^aIncluding those employed full time or part time.

^bExcluding retired individuals and those who declined to answer.

- 4 patients switched from fingolimod to an iDMT.
- Reasons patients cited for switching were hepatic side effects (n=3) and occurrence of relapse (n=1) (**Table 2**).
- 17 patients switched from an iDMT to fingolimod before the 3-month cut-off (day 84) for reasons unrelated to efficacy or safety.
- Reasons included inconvenient administration (n=7), needle phobia (n=4), frequency of injections (n=3) and 'other' (n=3).
- In the sensitivity analysis, excluding these patients who switched therapy did not impact the significance of the primary endpoint (**Figure 2b**).

Subgroup analyses

• Retention rates on randomized treatment in all subgroups analyzed were greater with fingolimod than with iDMTs, regardless of age, sex, race, disease status or treatment status (**Figure 3**).

Conclusions

- The significantly greater rate of treatment retention observed with fingolimod than with iDMTs in PREFERMS was sustained in both sensitivity and subgroup analyses.
- If patients exhibit poor adherence to iDMTs, switching them to fingolimod, if indicated, may improve adherence.

Figure 2. Retention rates in PREFERMS. a) Analysis in the FAS³ and b) sensitivity analysis in the FAS excluding patients who switched treatment for



References

1. Devonshire V et al. Eur J Neurol. 2011:18:69-77 2. Patti F. Patient Prefer Adherence 2010;4:1-9.

3. Cree B et al. *Neurology*. 2016;86(Suppl. 16):P3.115.

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