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Impact of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod: Subgroup analyses of the Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study

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Disease-modifying therapy;
Fingolimod;
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Abstract
Background: Fingolimod is a once-daily, oral sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing multiple sclerosis.
Objective: This post-hoc analysis of phase 3 FREEDOMS data assessed whether the effects of fingolimod are consistent among subgroups of patients defined by prior treatment history.
Methods: Annualized relapse rate and safety profile of treatment with fingolimod 0.5 mg, 1.25 mg, or placebo once-daily for 24 months were analyzed in 1272 relapsing multiple sclerosis

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Treatment history;
Relapse rate

patients, by subgroups based on disease-modifying therapy history (treatment-naive; prior interferon-β or glatiramer acetate), reason for discontinuation of prior disease-modifying therapy (unsatisfactory therapeutic response or adverse events), and prior disease-modifying therapy duration.

Results: Both fingolimod doses significantly reduced annualized relapse rate in patients that received prior interferon-β or glatiramer acetate, discontinued prior disease-modifying therapy owing to unsatisfactory therapeutic effect, were treatment-naive, or had prior disease-modifying therapy duration of >1–3 years ($P \leq 0.0301$ for all comparisons vs placebo). Fingolimod 1.25 mg resulted in greater reductions in annualized relapse rate in patients that discontinued prior disease-modifying therapy for adverse events or had prior disease-modifying therapy duration of ≤1 year or >3 years ($P \leq 0.0194$ vs placebo).

Conclusions: Fingolimod demonstrated similar efficacy in relapsing multiple sclerosis patients regardless of prior treatment history. Clinicaltrials.gov identifier: NCT00289978.

1. Introduction

Despite the widening array of disease-modifying therapies (DMTs) for multiple sclerosis (MS), individual responses to DMTs are variable and discontinuation of therapy remains common (Reynolds et al., 2010). Rates of discontinuation after 1–3 years of treatment with a DMT have historically ranged between 30% and 40% (Haas and Firzlaff, 2005; Milanese et al., 2005; Reynolds et al., 2010; Ruggieri et al., 2003). Consistent with this finding, rates of DMT persistence, defined as a lack of a 90- or 120-day gap in medication supply, fall from more than 70% after 6 months of treatment to less than 50% at 2 years (Kleinman et al., 2010; Wong et al., 2011). Common reasons for DMT discontinuation and poor adherence include lack of efficacy, intolerable side effects, or injection-related reasons (Arroyo et al., 2011; Devonshire et al., 2011; Haas and Firzlaff, 2005; Ruggieri et al., 2003; Turner et al., 2009; Visser and van der Zande, 2011). Furthermore, the efficacy of interferon (IFN) β may wane with the development of neutralizing antibodies over time (The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, 1996; Malucchi et al., 2004; Perini et al., 2004; Rudick et al., 1998; Sorensen et al., 2003, 2006).

Switching to another DMT is an effective strategy to manage patients who have suboptimal responses to an initial DMT (Carra et al., 2008). Rates of DMT switching are low compared with rates of discontinuation (e.g., 3–18% vs 30–40%) (Milanese et al., 2005; Reynolds et al., 2010; Wong et al., 2011). Reasons for the relatively low rate of switching are multifactorial and often depend on external factors including the lack of availability of alternative therapies; however, as more treatment options are becoming available for patients, switching is likely to become more common.

Fingolimod is an oral sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing MS at a dose of 0.5 mg once daily. The efficacy and safety of fingolimod were established in 2 pivotal trials. In the 2-year phase 3 Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study, the annualized relapse rate (ARR) was significantly reduced with once-daily treatment with fingolimod 0.5 mg or fingolimod 1.25 mg compared with placebo (−54% and −60%, respectively; $P<0.001$ for both comparisons vs placebo) (Kappos et al., 2010). In the 12-month, phase 3 Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) study, the ARR was reduced by treatment with once-daily fingolimod 0.5 mg and fingolimod 1.25 mg compared with once-weekly interferon (IFN) β-1a intramuscularly (IM) 30 μg (−52% and −38%, respectively; $P<0.001$ for both comparisons of fingolimod vs IFNβ-1a IM) (Cohen et al., 2010).

The aim of this post-hoc analysis was to assess the efficacy and tolerability of fingolimod in subgroups defined by prior treatment history. Using FREEDOMS trial data, this analysis compares the efficacy and safety of fingolimod in patients with or without prior DMT (including IFNβ and glatiramer acetate [GA]), and in patients who discontinued their prior DMT due to unsatisfactory therapeutic response or intolerable side effects. The potential effects of prior DMT treatment duration on fingolimod safety or efficacy were also examined.

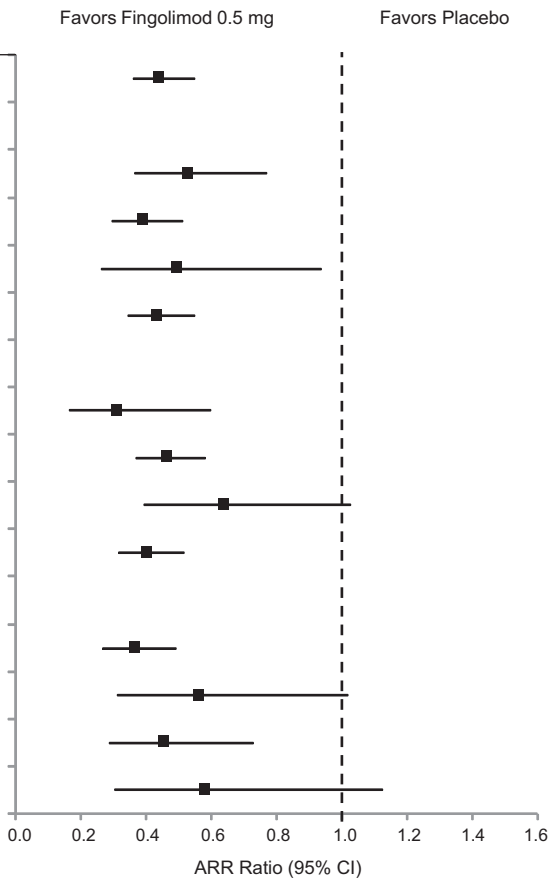
2. Material and methods

2.1. Study design

The FREEDOMS study design has been described in detail elsewhere (Kappos et al., 2010). This was a randomized, double-blind, placebo-controlled Phase 3 study. Key eligibility criteria were an age of 18–55 years and clinically active relapsing MS, defined by ≥1 documented relapse in the previous year or ≥2 relapses in the previous 2 years and a score of 0–5.5 on the Expanded Disability Status Scale (EDSS). Those patients who were previously treated with IFNβ or GA therapy had to have been discontinued ≥3 months before randomization; those previously treated with natalizumab had to have been discontinued ≥6-months prior. Patients were not asked to discontinue their prior DMT for study participation (they had already done so), and prior treatment with a DMT was not required for participation. Patients indicated their reason for discontinuation of prior DMT as unsatisfactory therapeutic effect, adverse event (AE), or other.

Patients were randomly assigned 1:1:1 to receive oral fingolimod at a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. Clinical assessments were performed at screening and at randomization (baseline), and study visits were scheduled in standard frequency at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months

Subgroup	N*	ARR			P
		Fingolimod 0.5 mg	Placebo	Reduction vs placebo, %	
Overall	843	0.18	0.40	54	<0.001
Treatment history					
Prior IFNβ	242	0.309	0.584	47	0.0008
IFNβ-naive	601	0.174	0.448	61	<0.0001
Prior GA	86	0.303	0.610	50	0.0301
GA-naive	757	0.204	0.469	56	<0.0001
Reason for prior DMT discontinuation					
UTE	79	0.291	0.931	69	0.0004
Reason other than UTE†	764	0.206	0.445	54	<0.0001
AE	152	0.329	0.517	36	0.0638
Reason other than AE†	691	0.191	0.476	60	<0.0001
Prior DMT duration, y					
No prior treatment	493	0.166	0.456	64	<0.0001
≤1	117	0.241	0.429	44	0.0565
>1–3	152	0.286	0.627	54	0.0011
>3	80	0.309	0.530	42	0.1083



AE=adverse event; ARR=annualized relapse rate; DMT=disease-modifying therapy; IFN=interferon; IM=intramuscular; GA=glatiramer acetate; UTE=unsatisfactory therapeutic effect.
*Intent-to-treat population; includes placebo and fingolimod 0.5 mg study arms.
†Includes DMT-naive patients.

Fig. 1 Annualized relapse rate ratios for fingolimod 0.5 mg (approved dose) vs placebo in subgroups based on prior treatment history.

after randomization; MS relapses could also be reported at any time during unscheduled visits. The primary endpoint was the ARR, defined as the number of confirmed relapses per year. To constitute a confirmed relapse, symptoms of a new or worsening neurologic abnormality must have been accompanied by an increase of at least half a point in the EDSS score, of at least 1 point in each of 2 EDSS functional system scores, or of at least 2 points in one EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems). Safety was assessed via AE reporting; physical exam and laboratory assessments were also conducted to monitor safety.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by each site's institutional review board and all patients gave written informed consent.

2.2. Analysis

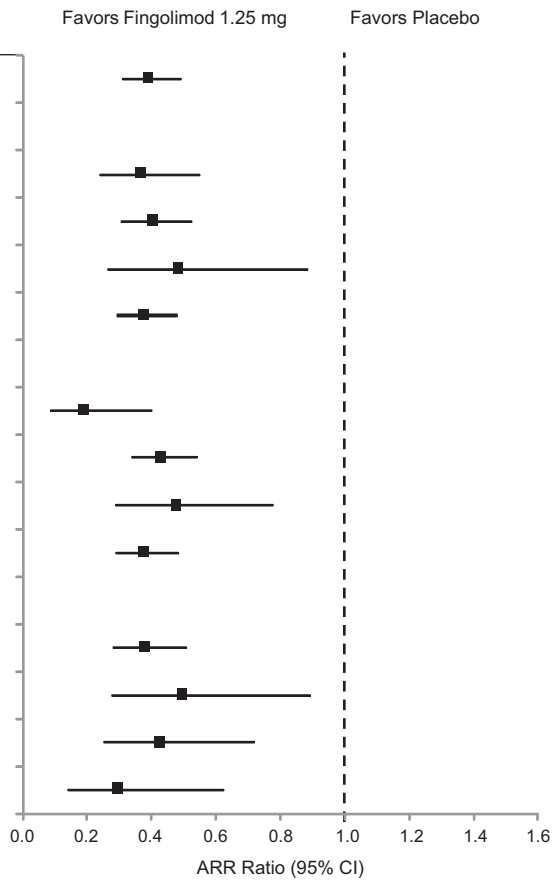
The effect of fingolimod on ARR was assessed in patient subgroups based on prior use of DMT, reason for discontinuation of prior DMT, and duration of prior DMT. The following subgroups were analyzed: (1) prior use of IFNβ therapy at any time in the patient's history, (2) prior use of GA therapy at any time in the patient's history, (3) discontinuation of prior DMT due to unsatisfactory therapeutic effect, (4) discontinuation of prior DMT due to adverse events (AE), and (5) duration of prior DMT (i.e., duration ≤ 1 year, >1–3 years, and >3 years). For comparison purposes, analyses were also performed in the complementary population (all remaining patients) for each subgroup: (1) patients with no prior use of IFNβ therapy, (2) no prior use of GA therapy, (3) no discontinuation of prior DMT due to unsatisfactory therapeutic effect or no prior DMT, (4) no discontinuation of prior DMT due to AEs or no prior DMT, and (5) no prior DMT. An interaction term between treatment and subgroup was included in the model to utilize information from all patients. Statistical analyses were conducted in the intent-to-treat (ITT) population using a negative binomial regression model adjusted for treatment, subgroup, and treatment-by-subgroup interaction. Post-hoc analyses were conducted for hypothesis generation only, with no adjustments for multiplicity. AE data refer to treatment-emergent AEs, regardless of causality.

3. Results

3.1. Patients

A total of 1272 patients were randomly assigned to treatment. Demographic and baseline disease characteristics for all subgroups are shown in Tables 1 and 2. A minority of all

Subgroup	N*	ARR			P
		Fingolimod 1.25 mg	Placebo	Reduction vs placebo, %	
Overall	847	0.16	0.40	60	<0.001
Treatment history					
Prior IFNβ	240	0.214	0.584	63	<0.0001
IFNβ-naive	607	0.181	0.448	60	<0.0001
Prior GA	96	0.296	0.610	52	0.0183
GA-naive	751	0.176	0.469	62	<0.0001
Reason for prior DMT discontinuation					
UTE	77	0.178	0.931	81	<0.0001
Reason other than UTE†	770	0.192	0.445	57	<0.0001
AE	159	0.246	0.517	52	0.0032
Reason other than AE†	688	0.178	0.476	63	<0.0001
Prior DMT duration, y					
No prior treatment	508	0.173	0.456	62	<0.0001
≤1	122	0.213	0.429	50	0.0194
>1–3	133	0.267	0.627	57	0.0013
>3	84	0.158	0.530	70	0.0013



AE=adverse event; ARR=annualized relapse rate; DMT=disease-modifying therapy; IFN=interferon; IM=intramuscular; GA=glatiramer acetate; UTE=unsatisfactory therapeutic effect.
*Intent-to-treat population; includes placebo and fingolimod 1.25 mg study arms.
†Includes DMT-naive patients.

Fig. 2 Annualized relapse rate ratios for fingolimod 1.25 mg vs placebo in subgroups based on prior treatment history.

patients had received previous treatment with any DMT (40.9%), with IFNβ (28.9%), with GA (10.8%), or with multiple DMTs (12.4%). Less than 5% of all patients had previously received immunosuppressive therapies.

3.2. IFNβ-naive patients vs those receiving prior IFNβ

A total of 367 patients had previously received IFNβ therapy. Patients previously treated with IFNβ had a longer duration of MS than IFNβ-naive patients (7.57 years vs 4.10 years), had more baseline gadolinium (Gd)-enhancing lesions (1.92 vs 1.43, respectively) and a greater mean baseline T2 lesion volume compared with IFNβ-naive patients (7523 mm^3 vs 5912 mm^3). Fingolimod 0.5 mg and 1.25 mg significantly reduced ARR compared with placebo in patients that received prior IFNβ treatment (−47% and −63%, respectively) and in those who were IFNβ-naive (−61% and −60%; Figs. 1 and 2).

3.3. GA-naive patients vs patients that received prior GA

A total of 138 patients had previously received GA. Patients with prior GA treatment had a longer duration of disease than those who were GA-naive (8.50 years vs 4.68 years). Both doses of fingolimod significantly reduced ARR compared with placebo in patients with prior GA treatment (−50% and −52%, for fingolimod 0.5 mg and 1.25 mg, respectively) and in those who were GA-naive (−56% and −62%, respectively; Figs. 1 and 2).

3.4. Prior DMT discontinuation owing to unsatisfactory therapeutic effect

A total of 118 patients cited unsatisfactory therapeutic effect as a reason for prior DMT discontinuation; it should also be noted that the subgroup of patients who did not discontinue for unsatisfactory therapeutic effect includes DMT-naive patients. Patients who discontinued their prior DMT for unsatisfactory efficacy tended to have a longer duration of MS (8.31 years vs 4.77 years), higher EDSS scores (3.08 vs 2.33), a greater number of Gd-enhancing lesions (1.90 vs 1.54), and greater T2 lesion volume (8552 mm^3 vs 6157 mm^3) than those who were DMT-naive or discontinued for other reasons (Table 1). However, the imbalances in patient subgroups were less pronounced in those randomized to fingolimod 0.5 mg than in the other treatment groups. Fingolimod had a marked effect in patients who experienced unsatisfactory efficacy with their previous DMT, lowering the ARR by 69–81% (Figs. 1 and 2).

Table 1 Baseline patient demographics and disease characteristics by prior treatment/discontinuation subgroup (randomized population).

	IFNβ-naive patients			IFNβ-treated patients		
	Fingolimod 0.5 mg (*n*=298)	Fingolimod 1.25 mg (*n*=304)	Placebo (*n*=303)	Fingolimod 0.5 mg (*n*=127)	Fingolimod 1.25 mg (*n*=125)	Placebo (*n*=115)
Demographic/disease characteristic						
Age, yr	36.3 (8.75)	37.0 (8.79)	37.2 (8.75)	37.1 (8.83)	38.3 (9.16)	37.4 (8.22)
Female, *n* (%)	206 (69.1)	208 (68.4)	217 (71.6)	90 (70.9)	87 (69.6)	81 (70.4)
Duration of MS[a], yr	3.92 (5.02)	4.03 (5.14)	4.34 (4.94)	6.92 (4.79)	8.34 (5.47)	7.44 (5.13)
Relapses in previous 1 yr, *n*	1.5 (0.72)	1.5 (0.76)	1.4 (0.72)	1.4 (0.86)	1.5 (0.93)	1.5 (0.75)
Relapses in previous 2 yr, *n*	2.1 (0.98)	2.0 (1.11)	2.1 (1.10)	2.3 (1.42)	2.4 (1.49)	2.4 (1.37)
EDSS score	2.26 (1.29)	2.26 (1.34)	2.33 (1.17)	2.39 (1.26)	2.78 (1.36)	2.91 (1.49)
Gd+lesions, *n*	1.38 (3.59)	1.80 (4.82)	1.11 (2.59)	2.28 (8.60)	1.80 (4.28)	1.65 (3.69)
T2 lesion volume, mm^3	5777 (7147)	6349 (7799)	5610 (6462)	6958 (8619)	8007 (9925)	7627 (8375)
Patients free of Gd+ lesions, *n* (%)	185 (62.1)	183 (60.8)	194 (64.2)	78 (61.9)	74 (60.2)	68 (59.6)
	GA-naive patients			**GA-treated patients**		
	Fingolimod 0.5 mg (*n*=383)	**Fingolimod 1.25 mg (*n*=377)**	**Placebo (*n*=374)**	**Fingolimod 0.5 mg (*n*=42)**	**Fingolimod 1.25 mg (*n*=52)**	**Placebo (*n*=44)**
Demographic/disease characteristic						
Age, yr	36.2 (8.75)	37.0 (9.02)	37.1 (8.73)	40.1 (8.25)	39.6 (7.79)	38.1 (7.45)
Female, *n* (%)	262 (68.4)	259 (68.7)	265 (70.9)	34 (81.0)	36 (69.2)	33 (75.0)
Duration of MS[a], yr	4.48 (4.98)	4.66 (5.23)	4.92 (5.11)	7.92 (5.53)	9.80 (6.08)	7.52 (5.16)
Relapses in previous 1 yr, *n*	1.5 (0.75)	1.4 (0.79)	1.4 (0.71)	1.4 (0.79)	1.7 (0.94)	1.5 (0.85)
Relapses in previous 2 yr, *n*	2.1 (1.12)	2.1 (1.22)	2.1 (1.10)	2.4 (1.23)	2.6 (1.36)	2.8 (1.67)
EDSS score	2.25 (1.30)	2.35 (1.36)	2.45 (1.25)	2.68 (1.05)	2.9 (1.31)	2.8 (1.58)
Gd+lesions, *n*	1.62 (5.48)	1.92 (4.85)	1.16 (2.61)	1.9 (6.47)	0.9 (2.90)	2.1 (4.84)
T2 lesion volume, mm^3	6149 (7629)	6841 (8496)	6120 (7171)	5932 (7654)	6740 (8537)	6521 (6372)
Patients free of Gd+ lesions, *n* (%)	233 (61.0)	220 (59.1)	235 (63.2)	30 (71.4)	37 (71.2)	27 (61.4)
	Discontinued prior DMT owing to unsatisfactory therapeutic effect			**Discontinued prior DMT for reason other than unsatisfactory therapeutic effect (includes DMT-naive patients)**		
	Fingolimod 0.5 mg (*n*=41)	**Fingolimod 1.25 mg (*n*=39)**	**Placebo (*n*=38)**	**Fingolimod 0.5 mg (*n*=384)**	**Fingolimod 1.25 mg (*n*=390)**	**Placebo (*n*=380)**
Demographic/disease characteristic						
Age, yr	38.5 (9.7)	37.8 (9.1)	38.9 (8.5)	36.4 (8.7)	37.3 (8.9)	37.1 (8.6)
Female, *n* (%)	31 (75.6)	31 (79.5)	29 (76.3)	265 (69.0)	264 (67.7)	269 (70.8)
Duration of MS[a], yr	7.16 (5.30)	9.33 (5.01)	8.48 (5.84)	4.57 (5.06)	4.88 (5.49)	4.86 (4.99)
Relapses in previous 1 yr, *n*	1.4 (0.7)	1.8 (1.0)	1.6 (1.0)	1.5 (0.8)	1.4 (0.8)	1.4 (0.7)
Relapses in previous 2 yr, *n*	2.4 (1.1)	2.9 (1.8)	2.7 (1.7)	2.1 (1.1)	2.1 (1.2)	2.1 (1.1)
EDSS score	2.49 (1.31)	3.22 (1.45)	3.59 (1.52)	2.27 (1.28)	2.33 (1.33)	2.38 (1.21)
Gd+lesions, *n*	1.03 (1.59)	2.30 (5.41)	2.45 (5.08)	1.71 (5.83)	1.75 (4.59)	1.14 (2.60)
T2 lesion volume, mm^3	7143 (8178)	9609 (10,290)	9007 (8767)	6022 (7566)	6564 (8266)	5876 (6842)
Patients free of Gd+ lesions, *n* (%)	23 (57.5)	20 (54.1)	20 (52.6)	240 (62.5)	237 (61.2)	242 (64.0)
	Discontinued prior DMT owing to AE			**Discontinued prior DMT for reason other than AE (includes DMT-naive patients)**		
	Fingolimod 0.5 mg (*n*=73)	**Fingolimod 1.25 mg (*n*=80)**	**Placebo (*n*=79)**	**Fingolimod 0.5 mg (*n*=352)**	**Fingolimod 1.25 mg (*n*=349)**	**Placebo (*n*=339)**
Demographic/disease characteristic						
Age, yr	38.2 (8.0)	37.8 (9.0)	38.2 (7.9)	36.2 (8.9)	37.2 (8.9)	37.0 (8.8)
Female, *n* (%)	56 (76.7)	57 (71.3)	56 (70.9)	240 (68.2)	238 (68.2)	242 (71.4)
Duration of MS[a], yr	6.60 (4.38)	7.83 (5.86)	7.19 (5.64)	4.57 (5.06)	4.88 (5.49)	4.86 (4.99)
Relapses in previous 1 yr, *n*	1.4 (0.8)	1.6 (0.9)	1.5 (0.7)	1.5 (0.76)	1.4 (0.78)	1.4 (0.70)
Relapses in previous 2 yr, *n*	2.2 (1.2)	2.5 (1.4)	2.4 (1.3)	2.1 (1.14)	2.1 (1.15)	2.1 (1.11)
EDSS score	2.22 (1.21)	2.49 (1.40)	2.58 (1.48)	2.31 (1.30)	2.40 (1.36)	2.46 (1.24)
Gd+lesions, *n*	1.29 (4.81)	1.18 (3.05)	1.26 (2.53)	1.72 (5.72)	1.94 (4.95)	1.26 (3.02)
T2 lesion volume, mm^3	5272 (6325)	5139 (6348)	6968 (7820)	6303 (7858)	7214 (8870)	5976 (6903)
Patients free of Gd+ lesions, *n* (%)	52 (72.2)	53 (67.1)	45 (57.7)	211 (59.9)	204 (59.1)	217 (64.2)

AE=adverse event; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; GA=glatiramer acetate; Gd+=gadolinium-enhancing; IFNβ= interferon beta; MS=multiple sclerosis.
All values are mean (SD) unless otherwise noted.
[a]Since diagnosis.

3.5. Prior DMT discontinuation owing to AEs

Prior DMT was discontinued owing to AEs in 232 patients; the subgroup of patients who did not discontinue because of AEs also includes DMT-naive patients. Baseline demographic and disease characteristics were similar between these subgroups, with the exception that patients who had discontinued prior DMT for AEs had a longer duration of disease than those who were DMT-naive or had discontinued for another reason (7.23 vs 4.77 years; Table 1). In patients who discontinued prior DMT owing to AE, the reduction in ARR with fingolimod 0.5 mg did not reach statistical significance (−36%, P=0.0638; Figs. 1 and 2), but did reach significance with fingolimod 1.25 mg compared with placebo (−52%, P=0.0032).

3.6. Duration of prior DMT

Baseline demographics and disease characteristics by duration of prior DMT is shown in Table 2. Across treatment groups, the duration of MS, EDSS scores, and T2 lesion volume increased as the duration of prior DMT increased. Relapse frequency was stable regardless of prior treatment duration. Patient characteristics were generally balanced between treatment subgroups, with 2 notable exceptions: MS disease duration tended to be higher in the fingolimod 1.25 mg group vs the other treatment groups in patients previously treated for >1-3 years, and was lower in the fingolimod 0.5 mg group in patients previously treated for >3 years. The number of Gd-enhancing lesions at baseline

Table 2 Baseline patient demographics and disease characteristics by duration of prior treatment (randomized population).

	Duration of prior treatment					
	No prior treatment			≤1 yr		
	Fingolimod 0.5 mg (n=244)	Fingolimod 1.25 mg (n=259)	Placebo (n=249)	Fingolimod 0.5 mg (n=49)	Fingolimod 1.25 mg (n=54)	Placebo (n=68)
Characteristic						
Age, yr	35.6 (8.76)	36.7 (8.91)	36.9 (8.82)	37.7 (7.85)	35.1 (9.14)	37.9 (8.34)
Female, n (%)	166 (68.0)	171 (66.0)	184 (73.9)	37 (75.5)	39 (72.2)	44 (64.7)
Duration of MS[a], yr	3.34 (4.70)	362 (5.13)	3.99 (4.95)	5.21 (4.85)	4.91 (4.44)	5.12 (4.40)
Relapses in previous 1 yr, n	1.5 (0.72)	1.5 (0.73)	1.4 (0.75)	1.6 (0.77)	1.4 (0.90)	1.4 (0.60)
Relapses in previous 2 yr, n	2.1 (0.97)	2.0 (1.12)	2.0 (1.09)	2.3 (1.05)	2.2 (1.11)	2.3 (1.13)
EDSS score	2.20 (1.31)	2.19 (1.29)	2.27 (1.14)	2.15 (1.25)	2.49 (1.38)	2.82 (1.22)
Gd+lesions, n	1.23 (3.32)	1.84 (4.95)	1.08 (2.47)	1.85 (5.46)	1.32 (3.42)	0.78 (2.02)
T2 lesion volume, mm^3	5283 (6714)	6657 (8148)	5185 (6027)	6984 (9009)	5919 (9267)	6777 (8062)
Patients free of Gd+ lesions, n (%)	153 (62.7)	154 (59.7)	156 (62.9)	32 (66.7)	34 (64.2)	51 (75.0)
	>1−3 yr			>3 yr		
	Fingolimod 0.5 mg (n=86)	Fingolimod 1.25 mg (n=67)	Placebo (n=66)	Fingolimod 0.5 mg (n=45)	Fingolimod 1.25 mg (n=49)	Placebo (n=35)
Characteristic						
Age, yr	36.9 (8.27)	39.8 (8.67)	36.6 (8.13)	39.4 (10.06)	39.8 (7.92)	39.9 (8.12)
Female, n (%)	60 (69.8)	48 (71.6)	44 (66.7)	32 (71.1)	37 (75.5)	26 (74.3)
Duration of MS[a], yr	6.86 (5.06)	8.09 (4.96)	7.03 (4.45)	8.42 (4.77)	10.68 (5.07)	10.41 (5.32)
Relapses in previous 1 yr, n	1.3 (0.81)	1.5 (0.89)	1.6 (0.82)	1.3 (0.83)	1.6 (1.0)	1.2 (0.51)
Relapses in previous 2 yr, n	2.2 (1.48)	2.4 (1.55)	2.5 (1.55)	2.0 (1.27)	2.4 (1.48)	2.1 (1.05)
EDSS score	2.48 (1.17)	2.83 (1.46)	2.83 (1.58)	2.59 (1.38)	2.97 (1.32)	2.76 (1.56)
Gd+lesions, n	2.88 (9.85)	1.85 (4.07)	1.98 (4.39)	1.33 (3.80)	2.06 (5.11)	2.09 (3.75)
T2 lesion volume, mm^3	7704 (8695)	7121 (8059)	7210 (7679)	6851 (8161)	8390 (9975)	9945 (9229)
Patients free of Gd+ lesions, n (%)	48 (55.8)	40 (60.6)	38 (58.5)	30 (66.7)	29 (61.7)	17 (48.6)

EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; MS=multiple sclerosis.
All values are mean (SD) unless otherwise noted.
[a]Since diagnosis.

was variable among treatment groups for patients with any prior exposure to a DMT.

Fingolimod 0.5 mg significantly reduced ARR in patients who were treatment-naive (−64%, $P<0.0001$) or who had received prior DMT for >1-3 years (−54%, $P=0.0011$). ARR reductions in patients with ≤1 year (−44%, $P=0.0565$) or >3 years of prior DMT (−42%, $P=0.1083$; Fig. 1) did not reach significance. Fingolimod 1.25 mg significantly reduced ARR in patients in all treatment duration categories (Fig. 2).

3.7. Safety

No specific safety issues were identified in any subgroup of patients. The overall incidence of AEs was similar in subgroups based on prior treatment history with IFNβ, and was slightly higher in patients that had received prior GA therapy compared with GA-naive patients (Supplementary Table 1). The incidence of AEs was slightly higher in patients who discontinued prior DMT owing to AE, regardless of treatment randomization in FREEDOMS (fingolimod or placebo). In patients who had discontinued prior DMT owing to unsatisfactory therapeutic effect, the incidence of nausea was higher with fingolimod 0.5 mg and 1.25 mg vs placebo (22.0% and 20.5% vs 5.3%, respectively). The incidence and type of AEs were similar among patients regardless of the duration of prior treatment (Supplementary Table 2).

The incidence of serious AEs is shown in Table 3. Notably, prior treatment with IFNβ or GA, discontinuation for unsatisfactory therapeutic effect, or discontinuation of prior therapy owing to AEs was not associated with an increase in the incidence of serious AEs of heart rhythm changes, increased liver enzymes, macular edema, or infections. No particular serious AE occurred with notably increased incidence in the group who discontinued their prior therapy due to AE. No trends in serious AE type according to treatment duration emerged.

4. Discussion

Previous subgroup analyses of FREEDOMS data showed the superior efficacy of fingolimod 0.5 mg vs placebo in most subgroups of patients based on baseline demographic characteristics (e.g., age, sex, treatment history [treatment-naive or previous DMT]), disease characteristics (number of relapses in the past year, past 2 years; disability, number of Gd-enhancing lesions, and T2 lesion volume) and disease activity (Devonshire et al., 2012). The current subgroup analyses extend those findings by evaluating additional factors that might affect response to fingolimod. These analyses evaluated the efficacy and safety of fingolimod 0.5 and 1.25 mg in subgroups differentiated by prior use of IFNβ or GA, reasons for discontinuation of prior DMT, and prior DMT duration. The data demonstrate that fingolimod was effective in patients with or without a history of IFNβ or GA treatment; however, the treatment effect seemed numerically higher in IFNβ- or GA-naive patients than in those with prior IFNβ or GA treatment. Fingolimod 0.5 mg significantly reduced ARR in patients who discontinued prior DMT because of unsatisfactory therapeutic response; these results are consistent with available studies that have shown that switching to another DMT after treatment failure is usually associated with a decrease in relapse rates (Caon et al., 2006; Carra et al., 2008; Gajofatto et al., 2009). In the previous studies, switching between IFNβ regimens or between IFNβ and GA was associated with lower ARR in patients for whom a first DMT had failed.

Table 3 Serious adverse events by treatment history subgroup (safety population).

	Fingolimod 0.5 mg	Fingolimod 1.25 mg	Placebo
Incidence, *n* (%)			
Treatment history			
Prior IFNβ	13/127 (10.2)	18/125 (14.4)	15/115 (13.0)
IFNβ naive	30/298 (10.1)	33/304 (10.9)	41/303 (13.5)
Prior GA	6/42 (14.3)	6/52 (11.5)	7/44 (15.9)
GA naive	37/383 (9.7)	45/377 (11.9)	49/374 (13.1)
Reason for discontinuation of prior treatment			
UTE	3 (7.3)	4 (10.3)	7 (18.4)
Reason other than UTE[a]	40 (10.4)	47 (12.1)	49 (12.9)
AE	8 (11.0)	13 (16.3)	11 (13.9)
Reason other than AE[a]	35 (9.9)	38 (10.9)	45 (13.3)
Duration of prior treatment, yr			
0	22 (9.0)	27 (10.4)	32 (12.9)
≤1	8 (16.3)	6 (11.1)	12 (17.6)
>1-3	7 (8.1)	10 (14.9)	8 (12.1)
>3	5 (11.1)	8 (16.3)	4 (11.4)

AE=adverse event; GA=glatiramer acetate; IFN=interferon; UTE=unsatisfactory therapeutic effect.
[a]Includes treatment-naive patients.

This effect was more pronounced when there was a switch from 1 class of DMT to another.

The present FREEDOMS analysis also showed that fingolimod numerically improved ARR in patients who discontinued prior DMT due to AEs. This population had a higher overall incidence of AEs during the study, but the AE incidence and type were similar between the fingolimod and placebo treatment groups, indicating that patients who could not tolerate other DMTs were more prone to develop AEs irrespective of treatment.

The safety and tolerability profile of fingolimod makes it attractive for patients with a history of poor tolerance of prior DMTs. In the current analysis, AE incidence and type were generally comparable in patients who received fingolimod or placebo in all subgroups. Only nausea was more common in fingolimod-treated patients who had discontinued prior DMT due to unsatisfactory therapeutic effect (20.5–22.0%) than in placebo-treated patients in the same subgroup (5.3%); however, this subgroup had a smaller sample size ($n=156$), and the sample size was not powered for statistical comparison in these post hoc comparisons.

There are several limitations to this study. First, this was a post hoc analysis not powered for these analyses and no correction for multiple comparisons was done. Some of the subgroups included only a small number of patients, which corresponded with wide confidence intervals of some ARR ratio estimates, some of which crossed 1. Second, this clinical trial population is not representative of the entire MS population, as it was overwhelmingly white, excluded older (>55 years) patients and youths (<18 years), and included very few patients with other prior immunosuppressive therapy exposure. Ongoing phase 4 studies will provide post-marketing data and expand the knowledge of fingolimod efficacy and safety in patient populations with various treatment histories.

5. Conclusions

Fingolimod 0.5 mg was effective in patients who were treatment naive or who had discontinued treatment with IFNβ or GA, and in patients who discontinued their prior DMT owing to unsatisfactory therapeutic effect.

Conflict of interest

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2013.10.006.

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